



# ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 42

Alan R. Katritzky

Advances in

# Heterocyclic Chemistry

Volume 42

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Advances in  
**HETEROCYCLIC  
CHEMISTRY**

*Edited by*

**ALAN R. KATRITZKY, FRS**

*Kenan Professor of Chemistry  
Department of Chemistry  
University of Florida  
Gainesville, Florida*

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## Preface

The present volume consists of five chapters. The first, by V. P. Mamaev and his colleagues, O. P. Shkurko and S. G. Baram, gives an account of the electronic effects of heteroaromatic and substituted heteroaromatic groups. It was with great sorrow that we learned of Professor Mamaev's untimely death late last year. This chapter, which will be a great utility to heterocyclic chemists, is thus his last major publication. We will remember him for it.

In chapter 2, István Hermecz has summarized our knowledge of the chemistry of the pyrimidoazepines, in particular that of diazabicyclo-undecene (DBU).

Chapter 3 is concerned with Claisen rearrangements in heteroaromatic systems and updates an article that appeared in Volume 8 of this series 20 years ago.

T. Kametani and S. Hibino have contributed an account of the synthesis of natural products by hetero Diels–Alder cycloaddition reactions, a subject to which they have contributed extensively.

The final chapter is concerned with the application of mass spectral techniques in heterocyclic chemistry, in particular to carbohydrates and other oxygen heterocycles, and is authored by J. R. Jocelyn Paré, K. Jankowski, and J. W. ApSimon.

ALAN R. KATRITZKY



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# Electronic Effects of Heteroaromatic and Substituted Heteroaromatic Groups

V. P. MAMAEV, O. P. SHKURKO, AND S. G. BARAM

*Institute of Organic Chemistry,  
Academy of Sciences of the U.S.S.R.,  
Siberian Division, Novosibirsk 630090, U.S.S.R.*

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## I. Introduction

Organic chemists must frequently predict the chemical reactivity, equilibrium state, and various physical characteristics of many functional groups in heterocyclic systems. This can be done by correlation analysis within the framework of  $\rho\sigma$ -approach. Reviews published during the past two decades in *Advances in Heterocyclic Chemistry* have covered the various aspects of using these correlations in the heterocyclic series (64AHC(3)209; 76AHC(20)1). Some generalizations have also been made in a number of monographs (73MI1; 74MI1; 78MI1; 85MI1). The problems discussed in these reviews and monographs can be roughly divided into three groups.

1. The effects of annular heteroatoms on the properties of functional derivatives of heterocycles;
2. The effects of whole heterocyclic fragments on the properties of functional side-chain derivatives of heterocycles;
3. The effects of substituents in heterocycles on the properties of both heterocycles themselves (including the heteroatoms in these rings) and functional groups.

Each of these three aspects has a significance of its own and the approaches used to study them are different. In the reviews cited above, the main attention was focused on aspects 1 and 3, whereas studies on the effects of heterocyclic fragments as substituents have not yet been sufficiently generalized.

This article is designed to fill this gap by systematizing the available data on the electronic effects of heteroaromatic groups as substituents. References are made only to the publications that contain quantitative characteristics of these effects both for the parent heteroaromatic groups and for those containing substituents in the heterocycle. Evidence is cited on traditional heteroaromatic substituents and, exceptionally, on some substituents that are partly hydrogenated or that contain prototropic tautomeric fragments that may formally be considered aromatic.

Within the limits of the topic under discussion, the electronic effects of heteroaromatic groups can be described quantitatively by a set of various  $\sigma$  constants. The most fundamental of these are the inductive constant  $\sigma_I$  and the

resonance constant  $\sigma_R$ . The  $\sigma_I$  constant characterizes the overall polar effect of a heteroaromatic group by combining the field (or direct) effect, which is of electrostatic nature, and the inductive effect transmitted from this group to the reaction site (or to any probe detectable by physical methods) through the consecutive polarization of electrons in  $\sigma$ - and  $\pi$ -bonds. Because of the difficulty in distinguishing between these constituents in practice, the term inductive effect is often used to cover both.

The resonance constant  $\sigma_R^\circ$  (sometimes referred to as a mesomeric constant) characterizes the mesomeric effect of a heteroaromatic group without its conjugation with a functional group mediated by an aromatic or other  $\pi$ -delocalized system. Mesomeric constants are successfully used in the NMR spectroscopy of aromatic and unsaturated compounds lacking these functional groups or in insulating reaction series. In other cases, depending on the character of the heteroaromatic substituent and  $\pi$ -delocalized framework and, hence, on the degree of conjugation, use is made of the resonance constants  $\sigma_R$ ,  $\sigma_R^-$ , and  $\sigma_R^+$ .

Use has recently been made of dual- and multiple-substituent parameter equations, which requires a precise knowledge of the values of inductive and resonance constants. The Hammett constants  $\sigma_m$  and  $\sigma_p$  can be readily calculated from the values of inductive and resonance constants, but they find a limited application. Such constants as  $\sigma^*$ ,  $\mathcal{F}$ , and  $\mathcal{R}$  are used even less often.

Authors often commit errors in terminology in confusing the effect of heterocyclic atoms (as endocyclic substituents in the benzene ring) with the effect of the entire heterocyclic fragment. The situation is aggravated by the fact that it is often very difficult to establish the real meaning of tabulated values of  $\sigma$  constants. In such cases, the answer can be obtained only by consulting the original paper (79M11).

This article does not deal with the steric effects of heteroaromatic groups. One can only presume them to be roughly the same or a little less than those in phenyl and other aromatic groups (77JOC3024). The influence of medium on the electronic effects of heteroaromatic groups presents a very serious problem. Studies made to determine the constants for many substituents, aryl groups among them, in various media clearly establish the validity of the  $\sigma_I$  values for use in a wide variety of aprotic and protic solvents, including water, pure alcohols, and water-alcohol mixtures. There are certain exceptions, such as charged (ionic) substituents and groups capable of forming hydrogen bonds with solvent molecules. These substituents include many heteroaromatic groups. Due to their polarity and to the presence of protophilic heteroatoms in the aromatic ring, the effects of nonspecific, and particularly specific, solvation become critical. This dependence is most strongly felt in the inductive effects of substituents. The values of these constants must therefore be used in calculations with great care, taking account of medium effects.

Evidence on the electronic effects of substituted heteroaromatic groups is, in our opinion, of greatest interest for researchers engaged in the field of synthetic organic chemistry, pharmaceutical and applied chemistry, and molecular spectroscopy. This evidence is therefore discussed separately (Section III). Another separate section (IV,B) deals with the peculiarities of the effect of substituents in the heteroaromatic ring and with the approaches to the *a priori* evaluation of inductive and resonance effects of such composite substituents.

This article covers publications up to the end of 1984 comprehensively, as well as some later papers.

## II. Electronic Effects of Unsubstituted Heteroaromatic Groups

### A. APPROACHES AND METHODS FOR EVALUATING ELECTRONIC EFFECTS OF HETEROAROMATIC GROUPS

To determine  $\sigma$  constants for heteroaromatic substituents, use is made of various physical parameters, as well as quantitative data on the reactivity of hetaryl, aliphatic, and aromatic compounds. Wide use has been made of NMR:  $\sigma$  constants for heteroaromatic groups are often determined by using  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{19}\text{F}$  chemical shifts in spectra of substituted benzenes (63JA709; 72BCJ1519; 79ZOR1737; 80AJC1763; 82MI1).

Comparison of  $\sigma$  constants calculated independently from the data on substituted fluorobenzenes, anilines, phenols, and monosubstituted benzenes in the same solvent makes it possible in most cases to conclude that they are in fairly good agreement.

Despite the success achieved by the  $^{19}\text{F}$ -NMR method in determining the substituent constants, opinions have been expressed as to the necessity of using  $^{19}\text{F}$  chemical shifts with more reserve (79JOC4766; 79OMR499). The presence of a fluorine atom in the benzene ring may lead to perturbations in the electronic structure of the benzene ring and direct polar conjugations between the substituent and the para fluorine, which may distort the electronic effects of the substituent under study and introduce an error in the  $\sigma$  constant values to be determined. Thus, in using the  $^{19}\text{F}$ -NMR method to evaluate  $\sigma$  constants, it is necessary to compare the values obtained with those determined by other methods.

The relative  $^{13}\text{C}$  chemical shifts of the meta and paracarbon atoms of monosubstituted benzenes can be regarded as ideal in dealing with the intramolecular interaction of the substituents and the unperturbed aromatic ring (76JA2020; 79DOK142; 79JOC4766; 80AJC1291).

An advantage of  $^{13}\text{C}$  NMR is that it is necessary to obtain only one phenyl derivative, whereas in using  $^{19}\text{F}$  (or  $^1\text{H}$ ) NMR one has to synthesize meta and para isomers of the fluorophenyl (or the aminophenyl and hydroxyphenyl) derivatives.

From the  $^{19}\text{F}$  spectra of fluorophenyl derivatives and  $^{13}\text{C}$  spectra of phenyl derivatives, one can determine the  $\sigma_1$  and  $\sigma_R^0$  constants for heteroaromatic groups; from the chemical shift values of amino and hydroxy group protons in the  $^1\text{H}$ -NMR spectra of aminophenyl and hydroxyphenyl derivatives, one can obtain other  $\sigma$  constants for heteroaromatic groups, in particular  $\sigma_R^-$  constants.

To estimate quantitatively the electronic effects of heteroaromatic groups, use is sometimes made of a correlation between the frequency or integral intensity of certain characteristic bands in the IR spectra of the compounds and the  $\sigma$  constants (68JA1757; 69CCC72; 70AG106; 72JCS(P2)158; 74JCS(P2)449; 75BAP923). Thus, for example, to determine the  $\sigma_m$  and  $\sigma_p$  constants for heteroaromatic groups, use is made of the dependences between the frequencies of the symmetrical and asymmetrical  $\text{NH}_2$  stretching vibration bands in substituted anilines (69CCC72; 74JCS(P2)449) or  $\text{NO}_2$  stretching vibration bands in substituted nitrobenzenes and the Hammett constants (75BAP923). It should be noted, however, that most of the  $\sigma_m$  and  $\sigma_p$  constants for heteroaromatic groups estimated from the  $\nu_s$  values differ markedly from the constants estimated from the  $\nu_{as}$  values even for the same solvent (75BAP923). In using the frequencies of characteristic oscillations there is the problem that the absorption band does not reflect the pure shape of the oscillation of a given structural fragment, but it contains additional shapes of oscillations occurring within this region of the spectrum, and overtones as well.

The accuracy of correlation between the  $\sigma$  constants and the intensity of bands is not high, as a rule, particularly in the case of strongly electron-withdrawing or electron-donating substituents. This results in an extremely rare application of these dependences to evaluate the  $\sigma$  constants for heteroaromatic groups.

There are instances when  $\sigma_m$  and  $\sigma_p$  constants for pyridyl groups were estimated by polarographic reduction of substituted azo- and nitrobenzenes (using the dependences between the half-wave potentials and the  $\sigma$  constants for substituents) (75BAP57; 75BAP797). The  $\sigma$  values obtained by polarography vary considerably, depending on the medium, compound type, and conditions of measurements. Therefore, polarographic reduction is not suitable for the quantitative estimation of  $\sigma$  constants for substituents.

The  $\sigma$  constants for heteroaromatic groups were also estimated using other correlations, for example, between the substituent constants and UV frequencies of azo dyes in neutral and acidic media (68ZOB1001; 68ZOB1139;

73ZOB636). But this dependence is of little use due to wide absorption bands in the UV spectra of azo dyes.

Besides the various physical methods,  $\sigma$  constants for heteroaromatic groups are often evaluated by using the quantitative reactivity data of heteroarylaliphatic and aromatic compounds: solvolysis rate constants of 1-arylethyl acetates and arylisopropyl chlorides (71JCS(B)2304; 72JCS(P)158); ionization constants of substituted benzoic acids (68ZOB1001; 70JCS(B)1595; 71JCS(B)2302), substituted phenols (69CCC72), anilines (69CCC72), and substituted acetic acids (64JOC1222; 81KGS1654), where the heteroaromatic groups are regarded as substituents.

The  $\sigma$  constants obtained from physical parameters and those calculated from quantitative data on reactivity are usually in satisfactory agreement. Some differences in the  $\sigma$  values can be accounted for mainly by the effect of solvents. In different solvents, particularly those with high polarity and a tendency to form hydrogen bonds, the substituent (in this case the heteroaromatic group) may be solvated. Different heteroaromatic groups are characterized by different susceptibilities to solvation, and solvation is differently reflected on their electron-withdrawing and -donating properties. Thus, in estimating and comparing the  $\sigma$  constants for heteroaromatic groups, solvent effects should be considered.

Attempts have also been made to calculate theoretically the  $\sigma_p$  constants for the pyridyl and protonated pyridyl groups (75BAP923). But these  $\sigma$  constants cannot serve as quantitative characteristics of the electronic effects of heteroaromatic groups due to the strong dependence on the particular quantum chemical parameters (coulomb and resonance integrals) used in the calculations.

Thus, in estimating various  $\sigma$  constants for heteroaromatic groups, the most reliable and convenient data are those on reactivity and physical parameters, especially the relative chemical shifts of meta and para carbon atoms of the benzene ring in  $^{13}\text{C}$ -NMR spectra of monosubstituted benzenes. Heteroaromatic groups are assumed to be substituents.

## B. ELECTRONIC EFFECTS OF SIX-MEMBERED HETEROAROMATIC GROUPS

AzinyI substituents are the most closely studied groups among the group of six-membered heteroaromatics. Azines belong to  $\pi$ -deficient systems. Their  $\pi$ -deficiency depends on the presence of electronegative nitrogen atoms in the aromatic ring and on the polarization of the  $\pi$ - and  $\sigma$ -electrons. AzinyI groups normally display electron-attracting properties (79KGS1155). The attraction of electrons is generally held to increase with consecutive substitution of

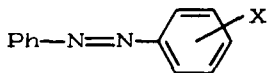
methyne fragments in the aromatic ring of the phenyl group by one, two, or more nitrogen atoms. This dependence, however, is of complicated character, since, in addition to the number of heteroatoms, an essential role is played by their position in the ring.

Systematic research into the inductive effects of pyridyl, diazinyl, and triazinyl groups carried out under identical conditions ( $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{19}\text{F}$  NMR, DMSO solvent) allowed the identification of the origin of separate contributions to their electronic effects, and revealed regularities for the entire series of azinyl groups (cf. Sections II,B,4 and II,B,5).

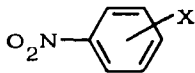
### 1. Pyridyl Groups

Some values for the same substituent constant estimated by different methods are found to be rather scattered (see Table I). The reason for the wide scatter in  $\sigma$  constants for pyridyl groups is that they were obtained via correlations of low sensitivity or statistical unreliability and that the measurements were made with various solvents having strong solvation effects (83KGS66).

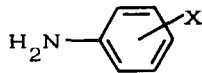
Attempts to use polarographic reduction of pyridylazobenzenes (series 1,  $\text{X} = \text{pyridyl}$ ) have shown it to be unsuitable for determining the substituent constants for pyridyl groups due to significant changes in their values depending on the solvent (75BAP57). Estimation of these constants by the reduction of nitrophenylpyridines (series 2,  $\text{X} = \text{pyridyl}$ ) results in obvious overestimations when measurements are made in such solvents as water and ethanol due to a specific solvation of the pyridine moiety. In the latter case, changes in the composition of the solvent (from 96% ethanol to pure water) produce considerable variations in the  $\sigma$  constants for unsubstituted pyridyl groups (cf. Table II) (75BAP797). However, polarographic reduction of nitrophenylpyridines in aprotic solvents such as DMF and DMSO gives values of the  $\sigma_1$  constants that are in good agreement with those obtained by NMR.



( 1 )



( 2 )



( 3 )

The Hammett constants for pyridyl groups were obtained according to Eq. (1) for DMSO solutions (or from an analogous equation for DMF solutions) and then the  $\sigma_1$  and  $\sigma_R^0$  values were calculated from Exner's linear relations between these constants [Eqs. (2) and (3)] (75BAP797).



TABLE I  
 $\sigma$  VALUES OF SUBSTITUENT CONSTANTS FOR PYRIDYL GROUPS

Type	Substituent, X			Method	Structural series (solvent)	Footnotes
	2-Py	3-Py	4-Py			
$\sigma_1$	0.404		0.274	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{N}=\text{NPh}$ (aq. EtOH)	<i>a</i>
	0.446		0.345	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{N}=\text{NPh}$ (aq. dioxane)	<i>a</i>
	0.210		0.426	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{N}=\text{NPh}$ (DMSO)	<i>a</i>
	0.283		0.241	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{N}=\text{NPh}$ (DMF)	<i>a</i>
	0.548	0.576	0.677	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ (aq.)	<i>b</i>
	0.593	0.704	0.754	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ (EtOH)	<i>b</i>
	0.158	0.190	0.295	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ (aq. dioxane)	<i>b</i>
	0.176	0.185	0.207	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ (DMSO)	<i>b</i>
	0.125	0.197	0.215	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ (DMF)	<i>b</i>
	0.20			$\text{pK}_a$	$\text{XCH}_2\text{COOH}$ (aq. EtOH)	<i>c</i>
	0.11	0.22	0.24	$^2J_{\text{HH}}$	$\text{XCH}=\text{CH}_2$	<i>d</i>
	0.08	0.22	0.18	$^1\text{H}$	$\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO)	<i>e</i>
	0.10	0.20	0.23	$^{13}\text{C}$	$\text{XPh}$ (DMSO)	<i>e</i>
	0.12	0.15	0.18	$^{13}\text{C}$	$\text{XCH}_2\text{Ph}$ (DMSO)	<i>f</i>
	0.10			$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ ( $\text{CH}_2\text{Cl}_2$ )	<i>g</i>
	0.11	0.18	0.19	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (DMSO)	<i>e</i>
$\sigma^*$	1.18	0.76	1.30	$E_{1/2}$	$\text{X}(\text{CH}=\text{CH})_n\text{Ph}$ (aq. EtOH)	<i>h</i>
	1.19	0.98	1.05	$\text{pK}_a$	$\text{XCH}=\text{NHNHC}(\text{NH}_2)=\text{NPh}$ (aq.)	<i>i</i>
$\sigma_R^\circ$	0.225		0.569	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{N}=\text{NPh}$ (aq. EtOH)	<i>a</i>
	1.106		0.171	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{N}=\text{NPh}$ (aq. dioxane)	<i>a</i>
	0.254		-0.034	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{N}=\text{NPh}$ (DMSO)	<i>a</i>
	0.000		0.076	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{N}=\text{NPh}$ (DMF)	<i>a</i>
	-0.009	-0.018	-0.037	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ (aq.)	<i>b</i>
	0.108	-0.033	0.016	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ (EtOH)	<i>b</i>
	0.070	0.102	0.005	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ (aq. dioxane)	<i>b</i>
	0.042	-0.005	-0.004	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ (DMSO)	<i>b</i>
	-0.005	-0.012	-0.026	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ (DMF)	<i>b</i>
	0.01	-0.05	-0.01	$^{13}\text{C}$	$\text{XPh}$ (DMSO)	<i>e</i>
	0.00			$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ ( $\text{CH}_2\text{Cl}_2$ )	<i>g</i>
	0.01			$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$	<i>j</i>
	-0.01	-0.07	-0.01	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (DMSO)	<i>e</i>
$\sigma_R^-$	0.27	0.03	0.26	$^1\text{H}$	$\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO)	<i>e</i>
$\sigma_{R(c)}^-$	0.31	0.31	0.45	$^{13}\text{C}$	$\text{XNHPh}$ (DMSO)	<i>k</i>
$\sigma_m$	0.490		0.490	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{N}=\text{NPh}$ (aq. EtOH)	<i>a</i>
	0.487		0.410	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{N}=\text{NPh}$ (aq. dioxane)	<i>a</i>
	0.307		0.413	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{N}=\text{NPh}$ (DMSO)	<i>a</i>
	0.283		0.270	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{N}=\text{NPh}$ (DMF)	<i>a</i>
	0.545	0.569	0.663	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ (aq.)	<i>b</i>
	0.552	0.691	0.760	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ (EtOH)	<i>b</i>
	0.158	0.229	0.297	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ (aq. dioxane)	<i>b</i>
	0.160	0.183	0.206	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ (DMSO)	<i>b</i>
	0.123	0.150	0.205	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ (DMF)	<i>b</i>
	0.33			$\text{pK}_a$	$\text{XC}_6\text{H}_4\text{COOH}$ (aq. EtOH)	<i>l</i>
	0.17	0.23	0.27	$^1\text{H}$	$\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO)	<i>e</i>

TABLE I (continued)

Type	Substituent, X			Method	Structural series (solvent)	Footnotes
	2-Py	3-Py	4-Py			
$\sigma_p$	0.355	0.000	0.376	$\nu_{s-\text{NO}_2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ ( $\text{CHCl}_3$ )	<i>m</i>
	0.000	0.000	0.000	$\nu_{s-\text{NO}_2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ ( $\text{CHBr}_3$ )	<i>m</i>
	0.324	0.485	0.324	$\nu_{as-\text{NO}_2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ ( $\text{CHCl}_3$ )	<i>m</i>
	0.318	0.421	0.688	$\nu_{as-\text{NO}_2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ ( $\text{CHBr}_3$ )	<i>m</i>
	0.686	0.833	0.682	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{N}=\text{NPh}$ (aq. EtOH)	<i>a</i>
	0.615	0.614	0.564	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{N}=\text{NPh}$ (aq. dioxane)	<i>a</i>
	0.495	0.471	0.448	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{N}=\text{NPh}$ (DMSO)	<i>a</i>
	0.323	0.310	0.350	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{N}=\text{NPh}$ (DMF)	<i>a</i>
	0.616	0.639	0.735	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ (aq.)	<i>b</i>
	0.691	0.760	0.875	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ (EtOH)	<i>b</i>
$\sigma_p^-$	0.251	0.319	0.342	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ (aq. dioxane)	<i>b</i>
	0.206	0.206	0.233	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ (DMSO)	<i>b</i>
	0.137	0.164	0.219	$E_{1/2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ (DMF)	<i>b</i>
	0.17			$\text{p}K_a$	$\text{XC}_6\text{H}_4\text{COOH}$ (aq. EtOH)	<i>l</i>
			0.743	$\text{p}K_a$	$\text{X}(\text{C}_4\text{H}_2\text{O})\text{CH}=\text{CHCOOH}$ (aq. methyl Cellosolve <sup>®</sup> )	<i>n</i>
	0.2			$^{13}\text{C}$	$2\text{-X}(\text{C}_5\text{H}_4\text{N})$ ( $\text{CS}_2$ )	<i>o</i>
	0.300	0.300	0.360	$\nu_{s-\text{NO}_2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ ( $\text{CHCl}_3$ )	<i>m</i>
	0.249	0.163	0.332	$\nu_{as-\text{NO}_2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ ( $\text{CHCl}_3$ )	<i>m</i>
	0.267	0.223	0.223	$\nu_{as-\text{NO}_2}$	$\text{XC}_6\text{H}_4\text{NO}_2$ ( $\text{CHBr}_3$ )	<i>m</i>
	0.66	0.62	0.66	LCMO		<i>m</i>
$\sigma_p^-$	0.35	0.25	0.44	$^1\text{H}$	$\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO)	<i>e</i>
$\sigma_{p(c)}^-$	0.55	0.58	0.81	$^{13}\text{C}$	$\text{XNHPh}$ (DMSO)	<i>k</i>
			0.73	$^{13}\text{C}$	$\text{XOPh}$ (DMSO)	<i>k</i>
$\mathcal{F}$	0.17	0.14		$\text{p}K_a$	$\text{XCH}=\text{NHNHC}(\text{NH}_2)=\text{NPh}$ (aq.)	<i>i</i>
	0.38			$\text{p}K_a$	$\text{XC}_6\text{H}_4\text{COOH}$ (aq. EtOH)	<i>l</i>
$\mathcal{R}$	-0.18			$\text{p}K_a$	$\text{XC}_6\text{H}_4\text{COOH}$ (aq. EtOH)	<i>l</i>

<sup>a</sup> (75BAP57).<sup>b</sup> (75BAP797).<sup>c</sup> (81MI1).<sup>d</sup> (81T929).<sup>e</sup> (83KGS66).<sup>f</sup> (80JOC105).<sup>g</sup> (76ZOB162).<sup>h</sup> (67MI1).<sup>i</sup> (85PHA356).<sup>j</sup> (79KGS1155).<sup>k</sup> (80JOC114).<sup>l</sup> (77JMC304).<sup>m</sup> (75BAP923).<sup>n</sup> (77CCC1871).<sup>o</sup> (68JPC2619).

TABLE II  
 MEDIUM EFFECT ON  $\sigma$  VALUES FOR PYRIDYL GROUPS<sup>a</sup>

Group	EtOH (%)	$\sigma_1$	$\sigma_R^\circ$	$\sigma_m$	$\sigma_p$
2-Py	0	0.548	-0.009	0.545	0.616
	10	0.277	0.140	0.330	0.457
	50	0.566	0.084	0.598	0.680
	75	0.787	-0.114	0.744	0.783
	96	0.593	0.108	0.552	0.691
3-Py	0	0.576	-0.018	0.569	0.639
	10	0.337	0.047	0.355	0.432
	50	0.628	-0.033	0.615	0.681
	75	0.770	-0.068	0.744	0.804
	96	0.704	-0.033	0.691	0.760
4-Py	0	0.677	-0.037	0.663	0.735
	10	0.387	0.117	0.432	0.559
	50	0.674	-0.072	0.647	0.697
	75	0.888	-0.169	0.824	0.844
	96	0.754	0.016	0.760	0.875

<sup>a</sup> Values obtained from polarography of nitrophenylpyridines in aqueous ethanol [from (75BAP797)].

$$E_{1/2} = 0.218\sigma - 0.589 \quad (r = 0.982) \quad (1)$$

$$\sigma_p = 1.14\sigma_1 + \sigma_R^\circ \quad (2)$$

$$\sigma_m = \sigma_1 + 0.38\sigma_R^\circ \quad (3)$$

To estimate the  $\sigma_m$  and  $\sigma_p$  constants for unsubstituted pyridyl groups, Pasternak and Tomasik attempted to use the dependence of the frequencies of symmetric ( $\nu_s$ ) and asymmetric ( $\nu_{as}$ )  $\text{NO}_2$  stretching vibrations in substituted nitrobenzenes (2) on the Hammett substituent constants (75BAP923). The pyridyl group constants obtained from the data of the IR spectra of the nitrophenyl pyridines in  $\text{CHCl}_3$  and  $\text{CHBr}_3$  have considerable scatter in their values depending on the solvent. Most of the  $\sigma_m$  and  $\sigma_p$  values estimated from  $\nu_{s-\text{NO}_2}$  differ widely from the respective values obtained from  $\nu_{as-\text{NO}_2}$  even for the same solvent. Four of the seven Hammett-type relationships used by the above authors to calculate the  $\sigma$  values have a low correlation coefficient ( $r = 0.949\text{--}0.965$ ). The method in question, just as polarography, is suitable only for a rough estimation of constants.

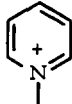

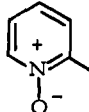
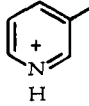
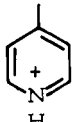
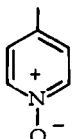
Pasternak and Tomasik attempted to calculate theoretically the  $\sigma_p$  constants for pyridyl and N-protonated pyridyl groups by using the relationship between the  $\sigma_p$  substituent constants and the  $D_p$  index [Eq. (4)], which

characterizes a degree of deviation of the  $\pi$ -bond order  $D_p$  of a given structure, compared with  $D_p$  magnitudes for the benzene molecule (75BAP923).

$$D_p = 1.0000 - 0.0691 |\sigma_p| \quad (r = 0.995) \quad (4)$$

The  $\sigma$  constants for pyridyl and N-protonated pyridyl groups thus obtained are listed in Tables I and III. The authors are of the opinion that these  $\sigma_p$  constants should not be regarded seriously because they are greatly dependent

TABLE III  
 $\sigma$  VALUES FOR POSITIVE CHARGED PYRIDYL GROUPS

Group X	$\sigma_m$	$\sigma_p$	Method	Structural series (solvent)	Footnotes
	1.02	0.96	$^1\text{H}$ $^{13}\text{C}$ $^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO) $\text{XPh}$ (DMSO) $\text{XC}_6\text{H}_4\text{F}$ (DMSO)	<i>a</i> <i>a</i> <i>a</i>
		0.75 0.67	$\text{pK}_a$ LCMO	$\text{XC}_6\text{H}_4\text{NH}_3^+$ (aq.)	<i>b</i> <i>c</i>
	0.23	0.27	$\text{pK}_a$	$\text{XC}_6\text{H}_4\text{NH}_3^+$ (aq.)	<i>b</i>
		0.62	LCMO		<i>c</i>
		0.65 0.67	$\text{pK}_a$ LCMO	$\text{XC}_6\text{H}_4\text{NH}_3^+$ (aq.)	<i>b</i> <i>c</i>
		0.33	$\text{pK}_a$	$\text{XC}_6\text{H}_4\text{NH}_3^+$ (aq.)	<i>b</i>

<sup>a</sup>  $\sigma_1$  is 1.09,  $\sigma_R^\circ$  is  $-0.13$  (81CCC584).

<sup>b</sup> (60JCS1511).

<sup>c</sup> (75BAP923).

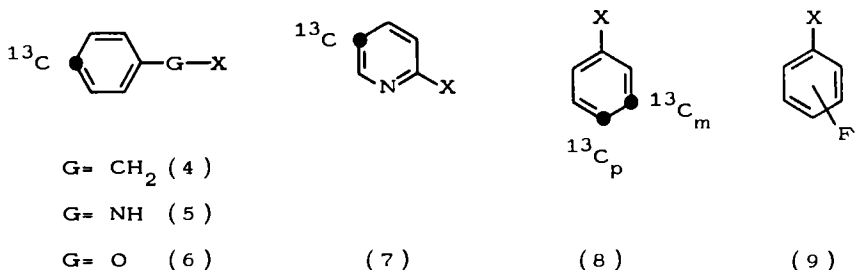
on the quantum chemical parameters (the coulomb and resonance integrals) assumed in the calculation.

The model compounds convenient for determining the substituent constants are aromatic amino derivatives (3), for which quantitative relationships are established between the  $\text{NH}_2$  chemical shift (solvent, DMSO) and the electronic effects of substituents in the benzene ring (79ZOR1737). Measurements of the  $\text{NH}_2$  chemical shifts for *m*- and *p*-aminophenylpyridines (series 3, X = pyridyl) with corrections for magnetic anisotropy of the pyridine ring make it possible to obtain a set of  $\sigma$  constants for pyridyl groups using Eqs. (5) and (6) (83KGS66).

$$\sigma_I = -1.332 \Delta\delta(\text{NH}_2\text{-}m) + 0.427 \Delta\delta(\text{NH}_2\text{-}p) + 0.008 \quad (5)$$

$$\sigma_R^- = 1.200 \Delta\delta(\text{NH}_2\text{-}m) - 1.129 \Delta\delta(\text{NH}_2\text{-}p) - 0.002 \quad (6)$$

In these equations  $\Delta\delta(\text{NH}_2)$  stand for the  $\text{NH}_2$  shifts relative to the resonance signal of aniline, with a positive sign corresponding to a shift toward high field.



Bradamante and Pagani used the empirical relationships between the  $^{13}\text{C}$ -para shifts in spectra of  $\alpha$ -substituted toluene (4), N-substituted anilines (5), O-substituted phenols (6), and the inductive and resonance constants for group X [Eqs. (7)–(9), respectively] (80JOC105; 80JOC114).

$$\delta(\text{C-p}) = 5.03\sigma_I + 126.97 \quad (7)$$

$$\Delta\delta(\text{C-p}) = 6.75270\sigma_I + 12.56006\sigma_R^- \quad (8)$$

$$\Delta\delta(\text{C-p}) = 6.28179\sigma_I + 8.69055\sigma_R^- \quad (9)$$

The  $\sigma_I$  values estimated from Eq. (7) for 2-, 3-, and 4-pyridyl groups agree well with the mean values for these groups (cf. Table VI, Section II,B,4). A set of  $\sigma_C^-$  (contiguous) constants was proposed to account for contiguous delocalization interactions between adjacent functionalities X and G in series (5) and (6). This set was shown to overlap with Hine's  $\sigma^-$  set for the majority of substituents, but it provides new values for substituents, including 4-pyridyl, in the Hammett and iso-Hammett series. A duality of the  $\sigma_R^-$  and

$\sigma_c^-$  values was recognized for the latter substituent depending on whether the adjacent group G is —O— or —NH— (80JOC114). Thus, they are not to be compared to the corresponding constants estimated by other methods.

In analyzing the  $^{13}\text{C}$ -NMR spectra of 2-substituted pyridines (7), Retcofsky and Friedel found the chemical shifts of the 5-carbon atom to be satisfactorily correlated with the Hammett  $\sigma_p$  constants for substituents located at the 2-position of the pyridine ring (68JPC2619). They used the corresponding correlation equation to estimate the  $\sigma_p$  constant for the 2-pyridyl group. The value of the C-5 chemical shift in the spectrum of 2,2'-bipyridyl (series 7, X = 2-pyridyl) has been estimated equivocally due to the closeness of the signals of C-5 and C-3. Therefore, the  $\sigma_p$  value for the 2-pyridyl group can only be regarded as approximate.

Of high reliability are the values of  $\sigma_1$  and  $\sigma_R^\circ$  constants calculated from the  $^{13}\text{C}$ -NMR spectra of phenylpyridines and based on the dependence of the chemical shifts of C-m and C-p atoms in the benzene ring in series (8) (82M11). In the corresponding Eqs. (10) and (11), the shifts relative to the benzene signal in the same solvent (DMSO) are taken with a correction for the magnetic anisotropy of the pyridine ring when X is pyridyl (83KGS66).

$$\sigma_1 = 0.308 \Delta\delta(\text{C-m}) + 0.011 \Delta\delta(\text{C-p}) + 0.019 \quad (10)$$

$$\sigma_R^\circ = -0.062 \Delta\delta(\text{C-m}) + 0.044 \Delta\delta(\text{C-p}) + 0.001 \quad (11)$$

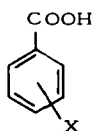
To determine the  $\sigma_1$  and  $\sigma_R^\circ$  values for pyridyl groups, use was also made of the well-known Taft equations [Eqs. (12) and (13)] and of the  $^{19}\text{F}$ -NMR data for *m*- and *p*-fluorophenylpyridines (series 9, X = pyridyl) (76ZOB162; 83KGS66).

$$\sigma_1 = [(0.6 - \Delta\delta(\text{F-m}))]/7.1 \quad (12)$$

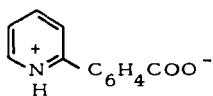
$$\sigma_R^\circ = [(\Delta\delta(\text{F-m}) - \Delta\delta(\text{F-p}))]/29.5 \quad (13)$$

On the whole, the methods used, i.e., the methods of  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{19}\text{F}$  NMR, as well as that of polarographic reduction of nitro compounds, give correlating results when DMSO is used as medium.

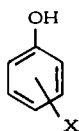
The  $\sigma_m$  and  $\sigma_p$  constants for the 2-pyridyl group found from the  $\text{p}K_a$  of pyridyl-2-benzoic acids (series 10, X = 2-pyridyl) in 50% eq. ethanol (77JMC304) appear to be questionable due to the possible manifestation of strong solvation effects and formation of zwitterionic structures 11. Hence



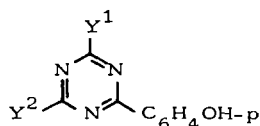
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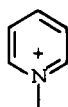
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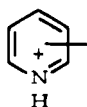
(13)

the  $\mathcal{F}$  and  $\mathcal{R}$  constants calculated on the basis of the Hammett equations will also be incorrect. And in other instances the overestimated values of the constants in hydroxy-containing solvents indicate the presence of strong specific solvation of pyridyl groups. By their electron-withdrawing properties such solvated groups are similar to protonated pyridyl groups (15).

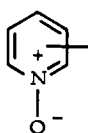
In spite of some apparent resemblance between the pyridinio (14) and the trimethylammonio groups, the former is more powerful as an inductive withdrawing substituent but it displays a small  $+M$  effect (81CCC584). On the whole, its electron-accepting properties are more significant than those of N-protonated pyridyl (15) and pyridyl *N*-oxide (16) groups (cf. Table III).



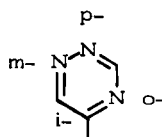
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
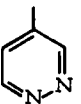

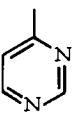

## 2. Diazinyl Groups

Numerous data on the reactivity of diazine compounds in reactions proceeding at the side chain, and some physical characteristics of these compounds, testify to the electron-withdrawing nature of diazinyl groups. The  $\sigma$  constants, however, are known only for pyridazinyl and pyrimidinyl groups. Pyridazinyl groups occupy a special place in the series of azinyl groups. In the pyridazine ring, two nitrogen atoms are directly bound with each other, resulting in a marked alternation of the lengths (77ACS(A)63) and orders of  $\pi$ -bonds (79CPB2105), and in a decrease of  $\pi$ -electron delocalization in the ring (74AHC(17)255).

In the pyrimidine ring, the interaction of the two annular nitrogen atoms is, by contrast, minimal and appears to be of additive character. Average values are reported for the inductive and mesomeric constants for pyrimidinyl groups (78KGS996). They have been calculated from the data on  $^{19}\text{F}$  spectra of fluorophenylpyrimidines (series 9,  $\text{X} = \text{pyrimidinyl}$ ) in  $\text{CCl}_4$ ,  $\text{CHCl}_3$ , acetone, and DMSO using Taft Eqs. (12) and (13). Even in these aprotic solvents, the effects of nonspecific solvation exert a marked influence on the  $\sigma_1$  values for pyrimidinyl groups (Table IV).

These constants may also be estimated by means of Eqs. (5), (10), (12), and (14) for correlating series 3, 8, 9, and 12, respectively. In using DMSO as a universal medium for such different correlation series, the scatter in the  $\sigma_1$  values decreases and the calculation of their average values becomes more

TABLE IV  
 $\sigma$  VALUES FOR DIAZINYL GROUPS

Group X	$\sigma_1$	$\sigma_R^\circ$ ( $\sigma_R^-$ )	$\sigma_m$	$\sigma_p^-$	Method	Structural series (solvent)	Footnotes
	0.18	(0.30)	0.28	0.48	$^1\text{H}$	$\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO)	<i>a</i>
	0.17	0.04			$^{13}\text{C}$	XPh (DMSO)	<i>a</i>
	0.21	(0.35)	0.36	0.59	$^1\text{H}$	$\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO)	<i>a</i>
	0.27	0.02			$^{13}\text{C}$	XPh (DMSO)	<i>a</i>
	0.06	(0.45)	0.23	0.53	$^1\text{H}$	$\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO)	<i>b</i>
	0.06	(0.45)			$^1\text{H}$	$\text{XC}_6\text{H}_4\text{OH}$ (DMSO)	<i>b</i>
	0.14	0.09			$^{13}\text{C}$	XPh (DMSO)	<i>c</i>
	0.10	0.10			$^{13}\text{C}$	XPh (acetone)	<i>c</i>
	0.05	0.10			$^{13}\text{C}$	XPh (acetone)	<i>d</i>
	0.12	0.09			$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (DMSO)	<i>b</i>
	0.07	0.09			$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (aprotic solvents)	<i>e</i>
	0.03	0.09	0.30	0.63	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ ( $\text{CCl}_4$ )	<i>f</i>
	0.13	(0.51)			$^1\text{H}$	$\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO)	<i>b</i>
	0.12	(0.47)			$^1\text{H}$	$\text{XC}_6\text{H}_4\text{OH}$ (DMSO)	<i>b</i>
	0.25	0.08			$^{13}\text{C}$	XPh (DMSO)	<i>c</i>
	0.25	0.09			$^{13}\text{C}$	XPh (acetone)	<i>c</i>
	0.17	0.09			$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (DMSO)	<i>b</i>
	0.20	0.09			$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ ( $\text{CCl}_4$ )	<i>g</i>
	0.21	0.09			$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (aprotic solvents)	<i>e</i>
	0.21	(0.18)	0.28	0.39	$^1\text{H}$	$\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO)	<i>b</i>
	0.21	(0.17)			$^1\text{H}$	$\text{XC}_6\text{H}_4\text{OH}$ (DMSO)	<i>b</i>
	0.30	-0.03			$^{13}\text{C}$	XPh (acetone)	<i>d</i>
	0.23	-0.04			$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (DMSO)	<i>b</i>
	0.28	-0.04			$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (aprotic solvents)	<i>e</i>

<sup>a</sup> (86KGS951).<sup>b</sup> (79ZOR1737).<sup>c</sup> (82MI1).<sup>d</sup> (83IZV299).<sup>e</sup> (78KGS996).<sup>f</sup> (80IZV1781).<sup>g</sup> (83MI1).



substantiated (cf. Table VI, Section II,B,4). Allowance for the magnetic anisotropy of pyrimidinyl groups in the  $^{13}\text{C}$ -NMR method (series 8) results in lower values of  $\sigma_i$  constants.

The mesomeric constants,  $\sigma_R^\circ$ , for pyrimidinyl groups estimated according to Eq. (13) proved to be practically independent of solvent polarity (78KGS996).

To estimate the resonance constants  $\sigma_R^-$  for the same groups use was made of Eq. (6) linking the  $\text{NH}_2$  chemical shifts in PMR spectra of *m*- and *p*-substituted anilines (3) with the resonance effects of substituents, and of a similar dependence [Eq. (15)] for hydroxy group protons in the spectra of substituted phenols (12) (79ZOR1737). In both cases the results were in good agreement.

$$\sigma_i = -1.007 \Delta\delta(\text{OH-}m) + 0.375 \Delta\delta(\text{OH-}p) + 0.006 \quad (14)$$

$$\sigma_R^- = 1.066 \Delta\delta(\text{OH-}m) - 1.160 \Delta\delta(\text{OH-}p) + 0.018 \quad (15)$$

To obtain the same set of  $\sigma$  constants for 3- and 4-pyridazinyl groups, only two correlation series were taken:  $\delta(\text{NH}_2)$  for series 3, and  $\delta(^{13}\text{C})$  for series 8 (86KGS951).






### 3. Triazinyl Groups

To determine the  $\sigma$  constants for the 2-*s*- and 3-*as*-triazinyl groups, use was made of the spectral data on the  $^1\text{H}$  NMR of aminophenyl- 3 and hydroxyphenyltriazines 12, the  $^{13}\text{C}$  NMR of phenyltriazines 8, and the  $^{19}\text{F}$  NMR of fluorophenyltriazines 9 (in these series  $X = \text{a triazinyl group}$ ). For 5- and 6-*as*-triazinyl groups, the constants were determined only from the data on the NMR spectra of phenyl- and aminophenyl-*as*-triazines (cf. Table V). The  $\sigma_p^-$  value for the *s*-triazinyl group was also calculated by Ohto *et al.* from the empirical dependence [Eqs. (26) and (27)] of the  $\sigma_p^-$  constants for substituted *s*-triazinyl groups on the  $\sigma_m$  constants for substituents in the triazine ring (74BJC1301). But such a calculation appears to be rather difficult because (1) these dependences have been obtained for disubstituted (hydroxyphenyl)triazines (13) having  $\text{Y}^1$  and  $\text{Y}^2$  as strongly electron-releasing groups, and (2) they take no account of the changes in the balance between the inductive and the resonance contributions to the total substituent effects transmitted through the triazine ring (cf. Section IV,C,1).

### 4. Inductive Effect of Azinyl Groups

The inductive influence of azinyl groups was considered from the viewpoint that there are two principal mechanisms of transmitting electronic effects of

TABLE V  
 $\sigma$  VALUES FOR TRIAZINYL GROUPS

Group X	$\sigma_1$	$\sigma_{\text{R}}^{\circ}$ ( $\sigma_{\text{R}}^{-}$ )	$\sigma_{\text{m}}$	$\sigma_{\text{p}}^{-}$	Method	Structural series (solvent)	Footnotes		
	0.09	(0.78)	0.39	0.88	$^1\text{H}$	$\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO)	<i>a</i>		
	0.12	(0.70)			$^1\text{H}$	$\text{XC}_6\text{H}_4\text{OH}_2$ (DMSO)	<i>a</i>		
	0.20	0.19			$^{13}\text{C}$	XPh (acetone)	<i>b</i>		
	0.20	0.19			$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (DMSO)	<i>a</i>		
	0.21	0.20			$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (aprotic solvents)	<i>c</i>		
			0.35	0.72					
	0.15	(0.56)	0.48	0.94	$^1\text{H}$	$\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO)	<i>f</i>		
	0.15	(0.53)			$^1\text{H}$	$\text{XC}_6\text{H}_4\text{OH}$ (DMSO)	<i>f</i>		
	0.17	0.12			$^{13}\text{C}$	XPh (DMSO)	<i>f</i>		
	0.20	0.11			$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (DMSO)	<i>f</i>		
	0.21	(0.69)	0.39	0.72	$^1\text{H}$	$\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO)	<i>f</i>		
	0.28	0.13			$^{13}\text{C}$	XPh (DMSO)	<i>f</i>		
	0.21	(0.50)	0.39	0.72	$^1\text{H}$	$\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO)	<i>f</i>		
	0.23	0.07			$^{13}\text{C}$	XPh (DMSO)	<i>f</i>		

<sup>a</sup> (80MI2).<sup>b</sup> (83TH1).<sup>c</sup> (78KGS996).<sup>d</sup> Calculated on Eq. (26) (74BCJ1301).<sup>e</sup> Calculated on Eq. (27) (74BCJ1301).<sup>f</sup> (87KGS257).

charged and polar groups through the  $\sigma$ -framework of molecules (87KGS672). One of these mechanisms is polarization, consecutively and progressively attenuated along the chain of  $\sigma$ -framework electrons under the influence of the substituent ( $\sigma$ -inductive effect,  $\chi_\sigma$ ). The other mechanism involves the direct field effect,  $F$ , of a charged or polar substituent which is transmitted through space directly to the reaction site or any other detectable probe. The ratio of the two mechanisms depends on many factors including the number of  $\sigma$ -bonds in the chain, the geometry of the molecular framework, the polarity and group electronegativity of the substituent, the nature of the reaction site, and the properties of the medium. When the substituent and the reaction site are separated by a system of  $\pi$ -bonds, the additional contributions caused by polarization of  $\pi$ -electrons by the action of heteroaromatic substituents with a

low inductive effect are assumed to be insignificant and to be contained as minor components in the principal constituents of the inductive effect. In practice, however, it is frequently difficult to separate these contributions from the resonance effect. As the phenyl group has an insignificant dipole moment and exerts no direct electrostatic action on the reaction site, the inductive influence of the group was attributed almost entirely to the  $\sigma$ -inductive effect (i.e.,  $\sigma_X \approx \sigma_1 = 0.13$ ). In the case of azinyl substituents, the group electronegativities and, hence, the  $\chi_\sigma$  effect increase additively as nitrogen atoms accumulate in the ring [Eq. (16)].

$$\sigma_X \approx 0.13 + \sum \sigma_{X(N)} \quad (16)$$

Nevertheless, as they possess a dipole moment, many azinyl groups may display a certain electrostatic effect. For molecules in which the detectable site is separated from an azinyl substituent by a benzene ring, the electrostatic constituent of the electronic effect of this substituent is estimated by Eq. (17),

$$\sigma_F = 0.003 - 0.031\mu \cos \theta \quad (17)$$

where  $\mu$  is the heterocycle dipole moment, and  $\theta$  is the angle between the direction of this dipole moment and the radius connecting the heterocycle center with the detectable site (87KGS672).

It has been shown in this work that the values contributed by endocyclic nitrogen atoms to the  $\sigma_X$  constant for the phenyl group are:  $\sigma_{X(2N)} = 0.02$  [for the ortho nitrogen atom relative to the ipso position; cf. Eq. (17)],  $\sigma_{X(3N)} = 0.01$  (for the meta nitrogen),  $\sigma_{X(4N)} \approx 0$  (for the para nitrogen). The satisfactory correlation is achieved for the azinyl  $\sigma_1$  values determined experimentally and calculated according to Eq. (18). These constant values are given in Table VI.

$$\sigma_1 = 0.133 + \sum \sigma_{X(N)} - 0.031\mu \cos \theta \quad (r = 0.956) \quad (18)$$

The division of the inductive effect of azinyl groups into two components explains the unexpectedly small  $\sigma_1$  values for the 2-pyridyl, 2-pyrimidinyl, and 3-as-triazinyl groups, as these components have opposite signs and largely cancel.

## 5. Resonance Effect of Azinyl Groups

$^{13}\text{C}$ -NMR spectra of phenylazines (8) and  $^{19}\text{F}$ -NMR spectra of fluoro-phenylazines (9) were used to estimate the  $\sigma_R^+$  constants for azinyl groups, and the PMR spectra of aminophenyl- (3) and hydroxyphenylazines (12) were used to find the  $\sigma_R^-$  constants. The former characterize the purely mesomeric

TABLE VI  
 $\sigma$  VALUES OF INDUCTIVE CONSTANTS FOR AZINYL GROUPS

Group	$\sigma_1$ determined <sup>a</sup>	Calculated values		
		$\sigma_1$	$\sigma_X$	$\sigma_F$
Phenyl	0.13	0.13	0.13	0
2-Pyridyl	0.10	0.12	0.15	-0.03
3-Pyridyl	0.19	0.18	0.14	0.04
4-Pyridyl	0.20	0.20	0.13	0.07
3-Pyridazinyl	0.18	0.16	0.16	0
4-Pyridazinyl	0.24	0.25	0.14	0.11
2-Pyrimidinyl	0.10	0.10	0.17	-0.07
4-Pyrimidinyl	0.18	0.18	0.15	0.03
5-Pyrimidinyl	0.22	0.22	0.15	0.07
3- <i>as</i> -Triazinyl	0.17	0.15	0.18	-0.03
5- <i>as</i> -Triazinyl	0.24	0.24	0.16	0.08
6- <i>as</i> -Triazinyl	0.22	0.20	0.17	0.03
2- <i>s</i> -Triazinyl	0.14	0.17	0.17	0

<sup>a</sup> Mean values in DMSO medium.

influence, while the latter describe polar conjugation involving the benzene ring of electron-attracting azinyl groups with electron-releasing amino and hydroxy functions (Table VII). The values of these constants were found to depend on the number of nitrogen atoms in the heteroaromatic ring and on their mutual arrangement (85MI2). The relative contributions of nitrogen heteroatoms ( $\sigma_{R(N)}^{\circ}$  and  $\sigma_{R(N)}^{-}$ ) to the resonance constants for azinyl groups (Table VIII) also allow these constants to be calculated for other azinyl groups (e.g., pyrazinyl, tetrazinyl). The satisfactory agreement between most values measured experimentally and those calculated with the help of the above increments points to an approximately additive character of the influence of nitrogen heteroatoms on the resonance effects of azinyl groups.

A clear-cut correlation has been recorded between the  $\sigma_R^{\circ}$  and  $\sigma_R^{-}$  values for each of the azinyl groups [Eq. (19)] (85MI2).

$$\sigma_R^{-} = 2.76\sigma_R^{\circ} + 0.25 \quad (r = 0.970) \quad (19)$$

The different effect of the nitrogen atoms from the ortho, meta, and para-positions (2-N, 3-N, 4-N) relative to the ipso carbon atom on the resonance constants for azinyl groups depends on the distribution of  $\pi$ -electron density over the heteroaromatic ring. The correlation of the resonance

TABLE VII  
 $\sigma$  VALUES OF RESONANCE CONSTANTS FOR AZINYL GROUPS

Group	$\sigma_R^{\circ}$		$\sigma_R^{-}$	
	Measured <sup>a</sup>	Calculated <sup>b</sup>	Measured <sup>a</sup>	Calculated <sup>b</sup>
Phenyl	-0.08	-0.08	0.04	0.04
2-Pyridyl	0.01	0.01	0.27	0.26
3-Pyridyl	-0.04	-0.05	0.03	0.12
4-Pyridyl	-0.01	0.00	0.26	0.29
3-Pyridazinyl	0.04	0.04	0.30	0.34
4-Pyridazinyl	0.02	0.03	0.35	0.37
2-Pyrimidinyl	0.09	0.10	0.45	0.48
4-Pyrimidinyl	0.09	0.09	0.49	0.51
5-Pyrimidinyl	-0.04	-0.02	0.18	0.20
3- <i>as</i> -Triazinyl	0.12	0.13	0.55	0.56
5- <i>as</i> -Triazinyl	0.13	0.12	0.69	0.59
6- <i>as</i> -Triazinyl	0.07	0.07	0.50	0.42
2- <i>s</i> -Triazinyl	0.19	0.18	0.74	0.73

<sup>a</sup> Mean values in DMSO medium.

<sup>b</sup> By means of respective increments (see Table VIII).

TABLE VIII  
 NITROGEN HETEROATOM INCREMENTS IN  
 RESONANCE CONSTANTS FOR AZINYL GROUPS

Position of nitrogen atom in ring <sup>a</sup>	$\sigma_{R(N)}^{\circ}$	$\sigma_{R(N)}^{-}$
2-N	0.09	0.22
3-N	0.03	0.08
4-N	0.08	0.25

<sup>a</sup> In respect to ipso carbon atom.

constants for azinyl groups with the  $\pi$ -electron charge at the corresponding positions in the ring have been shown to be of approximate character.

The inductive and resonance constants obtained can serve as a basis for estimating the generalized Hammett constants for azinyl groups. The values of  $\sigma_p^{-}$  constants are found to satisfactorily describe the equilibrium CH acidity of methyl- and acetylazines, as well as the NH acidity of aminoazines estimated in the medium of dipolar aprotic solvents (82ZOR9; 83ZOR465). The respective correlations are shown in Fig. 1.

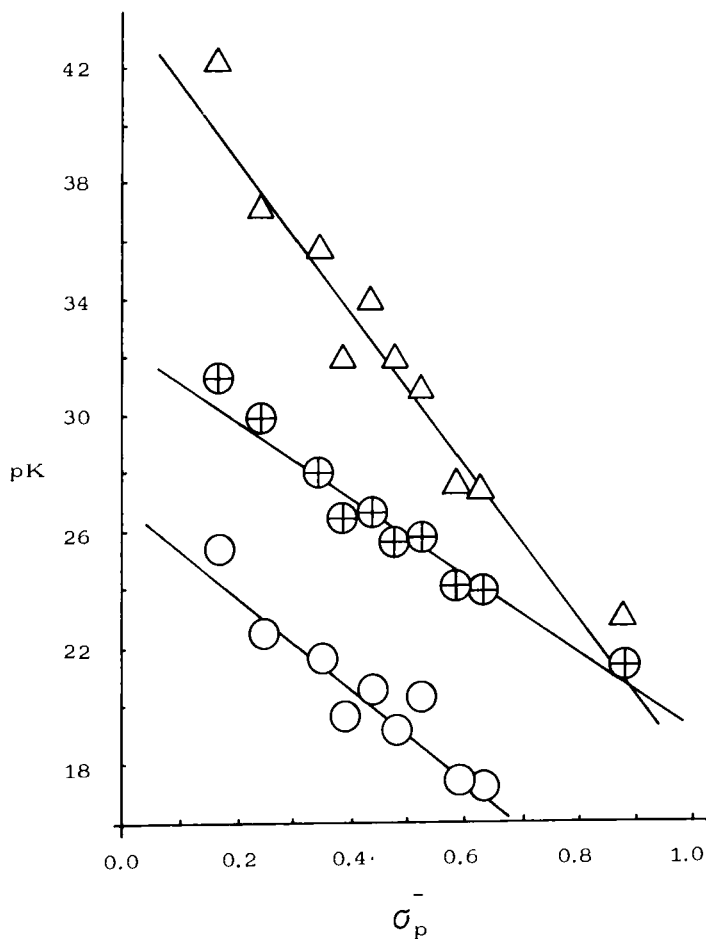


FIG. 1. Plot of pK values of azine derivatives versus  $\sigma_p^-$  for azinyl groups.  $\circ$ , Acetylazines, DMSO;  $\oplus$ , aminoazines, DMSO;  $\Delta$ , methylazines, DME.

### C. ELECTRONIC EFFECTS OF FIVE-MEMBERED HETEROAROMATIC GROUPS

#### 1. *Containing One Heteroatom*

Rather complete series of  $\sigma$  constants have been evaluated for the five-membered heteroaromatic substituents 2-furyl, 2-thienyl, 2-selenienyl, and 2-tellurienyl. The data are presented in Table IX.

TABLE IX  
 $\sigma$  VALUES FOR FIVE-MEMBERED HETEROAROMATIC GROUPS WITH ONE HETEROATOM

Type	2-Pyrrolyl	2-Furyl	3-Furyl	2-Thienyl	3-Thienyl	2-Selenienyl	2-Tellurienyl	Method	Structural series (solvent)	Footnotes
22	$\sigma_I$	0.09		0.12		0.15		$pK_a$	$XC_6H_4COOH$ (aq. EtOH)	<i>a</i>
		0.12		0.14				$^{19}F$	$XC_6H_4F$ ( $CH_2Cl_2$ )	<i>a</i>
		0.04		0.15				$pK_a$	$XCH_2COOH$ (aq. methyl Cellosolve <sup>®</sup> )	<i>b</i>
				0.21				$pK_a$	$XCH_2COOH$ (aq.)	<i>b</i>
		0.15		0.24				$^1H(J_{H-H})$	$XCH=CH_2$	<i>c</i>
		0.17	0.17	0.19				$pK_a$	$XCH_2NH_3^+$ (aq.)	<i>d</i>
		0.46						$pK_a$	$XCOOH$ (aq.)	<i>e</i>
			1.08	0.65	0.93	0.65		$\log k$	$XCOOEt$ (aq. acetone)	<i>f</i>
	$\sigma_R^\circ$						0.85	$\log k$	$XCOOEt$ (aq. acetone)	<i>g</i>
		-0.05		-0.06				$^{19}F$	$XC_6H_4F$ ( $CH_2Cl_2$ )	<i>a</i>
	$\sigma_R$	-0.05		-0.06				$^{19}F$	$XC_6H_4F$	<i>h</i>
		-0.08		-0.10		-0.14		$pK_a$	$XC_6H_4COOH$ (aq. EtOH)	<i>a</i>
	$\sigma_m$	-0.19		-0.19				$pK_a$	$XC_6H_4COOH$ (aq. EtOH)	<i>d</i>
		0.06		0.09	0.03			$pK_a$	$XC_6H_4COOH$ (aq. EtOH)	<i>i, j</i>
		0.09		0.08	0.03	0.06	0.06	$^1H$	$XC_6H_4OH$ (DMSO)	<i>k</i>
		0.05		0.08		0.09		$pK_a$	$XC_6H_4COOH$ (aq. EtOH)	<i>a</i>
	$\sigma_m^-$	0.09						$pK_a$	$XC_5H_4NH$	<i>l</i>
		0.13		0.11						<i>d</i>
		0.11		0.11	0.07	0.16	0.10	$pK_a$	$XC_6H_4OH$ (aq. EtOH)	<i>i, j</i>
		0.13		0.13	0.09	0.15	0.12	$^1H$	$XC_6H_4OH$ (DMSO)	<i>k</i>

23	$\sigma_m^+$		0.16	0.08			log $k$	XC <sub>6</sub> H <sub>4</sub> CMe <sub>2</sub> Cl (aq. acetone)	$m$
		0.10	0.15				log $k$	XC <sub>6</sub> H <sub>4</sub> CHMeOCOMe (aq. EtOH)	$n$
		0.10	0.15				$\nu_{C=O}$	XC <sub>6</sub> H <sub>4</sub> COMe (CCl <sub>4</sub> )	$n$
	$\sigma_p$	0.02	0.05	−0.02			pK <sub>a</sub>	XC <sub>6</sub> H <sub>4</sub> COOH (aq. EtOH)	$i, j$
		0.03	0.04	0.00	0.04	0.03	<sup>1</sup> H	XC <sub>6</sub> H <sub>4</sub> OH (DMSO)	$k$
		0.01	0.02		0.01		pK <sub>a</sub>	XC <sub>6</sub> H <sub>4</sub> COOH (aq. EtOH)	$a$
			0.02		0.01		pK <sub>a</sub>	2-X-hetaryl-5- COOH (aq. butyl Cellosolve* )	$o$
		0.00	−0.02						$d$
		−0.10					pK <sub>a</sub>	XC <sub>6</sub> H <sub>4</sub> COOH (aq. EtOH)	$p$
	$\sigma_p^-$	0.21	0.19	0.13	0.22	0.25	pK <sub>a</sub>	XC <sub>6</sub> H <sub>4</sub> OH (aq. EtOH)	$i, j$
		0.21	0.18	0.11	0.20	0.21	<sup>1</sup> H	XC <sub>6</sub> H <sub>4</sub> OH (DMSO)	$k$
	$\sigma_p^+$		−0.43	−0.38			log $k$	XC <sub>6</sub> H <sub>4</sub> CMe <sub>2</sub> Cl (aq. acetone)	$m$
		−0.39	−0.33				log $k$	XC <sub>6</sub> H <sub>4</sub> CHMeOCOMe (aq. EtOH)	$j, n$
		−0.45	−0.38				$\nu_{C=O}$	XC <sub>6</sub> H <sub>4</sub> COMe (CCl <sub>4</sub> )	$n$
	$\mathcal{F}$		0.10						$q$
	$\mathcal{R}$		0.04						$q$

<sup>a</sup> (76ZOB162).

<sup>b</sup> (64JOC1222).

<sup>c</sup> (81T929).

<sup>d</sup> (81MI1).

<sup>e</sup> (77JOC3024).

<sup>f</sup> (65RTC1169).

<sup>g</sup> (79JCS(P2)1347).

<sup>h</sup> (77KGS723).

<sup>i</sup> (70JCS(B)1595).

<sup>j</sup> (71JCS(B)2304).

<sup>k</sup> (80JCS(P2)971).

<sup>l</sup> (77CCC105).

<sup>m</sup> (71JCS(B)2302).

<sup>n</sup> (72JCS(P2)158).

<sup>o</sup> (70G777).

<sup>p</sup> (74CCC1711).

<sup>q</sup> (73JMC1207).



For a 2-pyrrolyl group only the values of  $\sigma_1$  and  $\sigma^*$  are known (77JOC3024; 81MI1). An *ab initio* calculation showed a 2-pyrrolyl group to be a stronger  $\pi$ -donor and  $\sigma$ -acceptor than a phenyl group (79NJC473). Investigation into the quaternization of some 5-hetarylpyrimidines as well as the reaction of their 2-chloro derivatives with piperidine has indicated a higher electron-releasing effect of a 2-(1-methyl)pyrrolyl group relative to other five-membered heteroaromatic groups (8OZN(B)463; 8OZN(B)468).

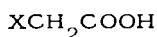
For the five-membered 3-hetaryl groups with one heteroatom in the ring, there are quantitative data on the electronic effects only for the unsubstituted 3-thienyl group (70JCS(B)1595; 71JCS(B)2302; 80JCS(P2)971) and  $\sigma^*$  constants for the 3-furyl group (65RTC1169).

Table IX lists the  $\sigma$  constants for unsubstituted five-membered 2- and 3-hetaryl groups estimated by different methods. The values of  $\sigma$  constants obtained from the data of IR,  $^1\text{H}$  and  $^{19}\text{F}$  NMR, and  $\text{pK}_a$ , are rather close to one another (except those of the  $\sigma_p$  constants). Some of the differences in the values of the  $\sigma$  constants can be accounted for by solvent effects. In addition, according to Yagupolskii *et al.* (76ZOB162) in using  $^{19}\text{F}$  NMR to estimate  $\sigma$  constants, these differences may also be due to the effect of the ring current of the  $\pi$ -electron system in hetaryls on fluorine atom screening. This effect is different from that in substituted fluorobenzenes, and this causes a change in the value of the chemical shift and hence in that of the corresponding  $\sigma$  constants obtained from this value. This effect is not great but in the case of the meta isomers it varies with the torsional angle between the benzene and the heteroaromatic rings. The higher values of  $\sigma_R$  constants for the 2-furyl and the 2-thienyl groups obtained from the  $\text{pK}_a$  data on substituted benzoic acids (series 10, X = 2-furyl, 2-thienyl) as compared to the values obtained by the  $^{19}\text{F}$  method are accounted for by the effect of direct polar conjugation of hetaryls with the carbonyl group (76ZOB162).

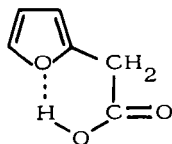
Fringuelli *et al.* report the  $\sigma$  constants to be independent of the type of reactions in question since in transmitting the electronic effect of a substituent located at the meta position relative to the reaction site, the resonance constituent is insignificant; for different  $\sigma_m$  constants ( $\sigma_m$ ,  $\sigma_m^+$ ,  $\sigma_m^-$ ) there occur some slight variations within experimental error limits (cf. Table IX), whereas the  $\sigma_p$  constants ( $\sigma_p$ ,  $\sigma_p^+$ ,  $\sigma_p^-$ ) differ considerably from one another (71JCS(B)2302; 71JCS(B)2304; 72JCS(P2)158; 80JCS(P2)971). The  $\sigma_p$  constants are a function of conjugation of the substituent with the reaction site in the transition state, so they are dependent on the type of reaction series. This accounts for the great discrepancy in the values of  $\sigma_p$  constants for five-membered heteroaromatic substituents determined from the data of different reaction series. In their total effect, all the five-membered 2-hetaryl groups under discussion are only weak electron-withdrawing substituents:  $\sigma_m$  and  $\sigma_p$ .

are positive, except for  $\sigma_p$  for the 2-furyl group ( $-0.10$ ), because of which the 2-furyl group is a weak electron-releasing substituent (74CCC1711).

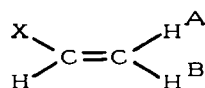
In their inductive and conjugative effects, the five-membered 2-hetaryl groups with one heteroatom in the ring are comparable with the phenyl group for which  $\sigma_1 = 0.08$  and  $\sigma_R^\circ = -0.09$ . The values of  $\sigma_1$  constants for five-membered 2-hetaryls increase somewhat in the sequence 2-furyl < 2-thienyl < 2-selenienyl ( $0.09, 0.12, 0.15$ ) according to Matyushecheva *et al.* (76ZOB162), while the electron-withdrawing ability of the heteroatom changes in the opposite sequence  $0 > S > Se$  ( $3.6; 2.5; 2.4$ ) (72JCS(P2)1738). The calculated total ( $\sigma + \pi$ ) charge at the  $\alpha$ -position in furan ( $0.1943$ ) (68T3285) is also higher than that in thiophene ( $-0.0546$ ) (68T2663). The  $\sigma_1$  constants for the 2-furyl and 2-thienyl groups were estimated by Charton from the data on ionization of hetarylacetic acids in water (series 18,  $X = 2$ -furyl, 2-thienyl) (64JOC1222).



( 18 )



( 19 )



( 20 )

In this instance, the lower value of the  $\sigma_1$  constant for the 2-furyl group relative to  $\sigma_1$  for the 2-thienyl group is attributed by the author to the stronger intramolecular hydrogen bond with the participation of an oxygen atom (structure 19) rather than sulfur. In other cases when the  $\sigma_1$  constants were determined from the data on the  $pK_a$  of substituted benzoic acids (series 10,  $X =$  hetaryl) in aqueous ethanol one of the possible reasons for the observed sequence of  $\sigma$  constants (2-furyl < 2-thienyl < 2-selenienyl) may be the effects of specific solvation (different tendency of furyl, thienyl, and selenienyl groups to form hydrogen bonds with solvent). But for the 2-thienyl group a higher value of the  $\sigma_1$  constant as compared to that for the 2-furyl group has also been obtained from the data on the  $^{19}F$  chemical shifts of fluorophenyl-hetaryls in dichloroethane (76ZOB162). According to Yagupolskii and co-workers the above sequence of the  $\sigma_1$  constants for 2-hetaryl groups cannot be accounted for by the electronegativity of heteroatoms or by solvation effects. It is due to other factors, of which the most probable are the value and direction of the dipole moment of the heterocyclic moiety and the preferred conformation of the molecule (76ZOB162).

The  $\sigma_1$  constants for the 2-furyl and 2-thienyl groups are estimated by Knorr with the aid of a single-variable parameter equation relating the constants of

spin-spin splitting ( $^2J_{\text{H}A_{\text{H}}B}$ ) of geminal protons (olefin **20**,  $X = 2\text{-furyl}$ ,  $2\text{-thienyl}$ ) with the  $\sigma_1$  constants for the  $X$  substituents (81T929) [Eq. (20)].

$$\sigma_1 = 0.15(\pm 0.005)(2.4 - ^2J) \quad (20)$$

The values of the  $\sigma_{\text{R}}^{\circ}$  constants for the 2-thienyl and the 2-furyl groups are in agreement with the  $\pi$ -electron charge at the  $\alpha$ -position of thiophene ( $-0.078$ ) (68T2663) and furan ( $-0.0674$ ) (68T3285). The presence of a certain torsional angle in a preferred conformation of 2-phenylthiophene as distinct from that of 2-phenylfuran considered to be coplanar (71T4947) does not seem to exert a decisive influence on the order of the  $\sigma_{\text{R}}^{\circ}$  constants for 2-furyl and 2-thienyl. This opinion is expressed by Yagupolskii and co-workers (76ZOB162).

Comparison of all the quantitative available data for the unsubstituted five-membered 2-hetaryl groups with a single heteroatom in the ring (Table IX) shows that if these hetaryls are conjugated with an electron-withdrawing group they display a strong electron-releasing effect ( $+M$  effect); but if conjugated with electron-releasing groups they display  $-M$  effects.

A comparison between the 2- and the 3-thienyl groups shows the latter to be an even weaker electron withdrawer than the former (see Table IX).

There are data characterizing quantitatively the electronic effects of the  $N$ -pyrrolyl group (Table X). To estimate the  $\sigma_1$  and  $\sigma_{\text{R}}^{\circ}$  constants for the  $N$ -pyrrolyl group, Fong used Eqs. (21) and (22) relating the chemical shifts of the meta and para carbon atoms in the  $^{13}\text{C}$ -NMR spectra of monosubstituted

TABLE X  
 $\sigma$  VALUES FOR  $N$ -PYRROLYL GROUP

$\sigma_1$ ( $\mathcal{F}$ )	$\sigma_{\text{R}}^{\circ}$ ( $\mathcal{R}$ )	$\sigma_o$	$\sigma_m$	$\sigma_p$	Method	Structural series (solvent)	Footnotes
0.345	$-0.210$				$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ ( $\text{CDCl}_3$ or $\text{CD}_3\text{CN}$ )	<i>a</i>
0.24	$-0.19$				$^{13}\text{C}$	$\text{XC}_6\text{H}_5$ ( $\text{CDCl}_3$ )	<i>b</i>
(0.50)	( $-0.09$ )		0.47	0.37	$\text{p}K_{\text{a}}$	$\text{XC}_6\text{H}_4\text{COOH}$ (aq. EtOH)	<i>c</i>
				0.10	$^1\text{H}$	$\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO)	<i>d</i>
				0.21	$\nu_{\text{as-NH}_2}$	$\text{XC}_6\text{H}_4\text{NH}_2$ ( $\text{CCl}_4$ )	<i>d</i>
		0.56		$-0.02$	$\text{p}K_{\text{a}}$	$\text{XC}_5\text{H}_4\text{NH}$	<i>e</i>

<sup>a</sup> (81JCR(S)364).

<sup>b</sup> (80AJC1763).

<sup>c</sup> (77JMC304).

<sup>d</sup> (74JCS(P2)449).

<sup>e</sup> (76MI1).

benzenes (series 8, X = *N*-pyrrolyl) with the  $\sigma$  constants for substituents (solvent  $\text{CDCl}_3$ ) (80AJ1763).

$$\Delta\delta(\text{C-m}) = 1.80\sigma_{\text{I}} - 1.42\sigma_{\text{R}}^{\circ} - 0.10 \quad (21)$$

$$\Delta\delta(\text{C-p}) = 5.71\sigma_{\text{I}} + 20.52\sigma_{\text{R}}^{\circ} - 0.61 \quad (22)$$

But these equations were shown by the author to give a low accuracy of  $\sigma$  constants ( $\pm 0.1$  for  $\sigma_{\text{I}}$  and  $\pm 0.03$  for  $\sigma_{\text{R}}^{\circ}$ ) mainly due to small differences in the amounts of chemical shifts ( $^{13}\text{C}$ ) of meta carbon atoms.

To determine the  $\sigma_{\text{I}}$  and  $\sigma_{\text{R}}^{\circ}$  constants for the *N*-pyrrolyl group Elguero *et al.* used the  $^{19}\text{F}$  method (81JCR(S)364). The  $\sigma_{\text{p}}$  constants for the *N*-pyrrolyl group were estimated by Elguero *et al.* both by IR spectroscopy (using the dependence between the frequencies of asymmetrical valence vibrations of the  $\text{NH}_2$  group in *p*-substituted anilines and the  $\sigma_{\text{p}}$  constants for substituents) [Eq. (23)] and by  $^1\text{H}$  NMR (using the dependence between the relative chemical shifts of protons in the  $\text{NH}_2$  group of *p*-substituted anilines and the  $\sigma_{\text{p}}$  constants for substituents) [Eq. (24)] (74JCS(P2)449).

$$\sigma_{\text{p}} = 3.11 \times 10^{-2} \Delta\nu_{\text{as}} + 12.6 \times 10^{-2} \quad (23)$$

$$\sigma_{\text{p}} = 1.25 \times 10^{-2} \Delta\delta(\text{NH}_2\text{-p}) + 3.06 \times 10^{-2} \quad (24)$$

The  $\sigma_{\text{p}}$  constants determined from the IR spectroscopic data are considered by the authors to be overestimated, possibly due to the formation of associates of pyrrolylaniline (74JCS(P2)449). The high value of the  $\sigma_{\text{p}}$  constants for the *N*-pyrrolyl group obtained from the  $\text{pK}_{\text{a}}$  of the *p*-(*N*-pyrrolyl)benzoic acid in aqueous ethanol (77JMC304) as compared with the respective value of the  $\sigma_{\text{p}}$  constant calculated from the NMR data (74JCS(P2)449) (Table X) is clearly accounted for by solvation effects.

## 2. Containing Two or More Heteroatoms

Of the unsubstituted five-membered heteroaromatic groups containing two and more heteroatoms in the ring, the available data mainly concern *N*-azolyl groups. Of the *C*-azolyl groups there is evidence on the 4(5)-imidazolyl group (81MI1), the 5-tetrazolyl group, its anion and cation (79JCS(P2)1670; 80MI3; 80MI4, 83KGS1130). These data are summarized in Table XI.

To determine the  $\sigma$  constants for the 5-tetrazolyl group, Shchipanov used correlations linking the acid-base properties of 5-substituted tetrazoles with  $\sigma$  constants for substituents regarding a 5-tetrazolyl group as one of the substituents (5,5'-ditetrazolyl) (83KGS1130). In the work of Kaczmarek *et al.* the  $\sigma$  constants for the 5-tetrazolyl group are determined by means of  $\text{pK}_{\text{a}}$  values of substituted phenyltetrazolyl acids, as well as by IR, UV, and PMR

TABLE XI  
 $\sigma$  VALUES FOR UNSUBSTITUTED AZOLYL GROUPS




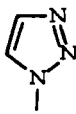
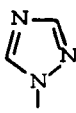

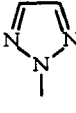
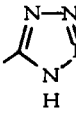

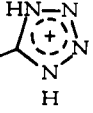
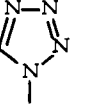
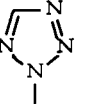
Group X	$\sigma_1$ ( $\sigma^*$ )	$\sigma_R^o$ ( $\sigma_R$ )	$\sigma_m$	$\sigma_p$	Method	Structural series (solvent)	Footnotes
	0.26	-0.36 -0.165		0.19 0.23	$A_{1640}$ $^{13}\text{C}$ $^1\text{H}$ $\nu_{\text{as-NH}_2}$ $^{19}\text{F}$	$\text{XCH=CH}_2$ ( $\text{CCl}_4$ ) $\text{XC}_6\text{H}_5$ ( $\text{CDCl}_3$ ) $\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO) $\text{XC}_6\text{H}_4\text{NH}_2$ ( $\text{CCl}_4$ ) $\text{XC}_6\text{H}_4\text{F}$ ( $\text{CDCl}_3$ or $\text{CD}_3\text{CN}$ )	<i>a</i> <i>b</i> <i>c</i> <i>c</i> <i>d</i>
	0.12				$\text{pK}_a$	$\text{XCH}_2\text{NH}_3^+$ (aq.)	<i>e</i>
	0.513 0.46 0.60	-0.155 -0.12		0.24 0.45	$^{19}\text{F}$ $^{13}\text{C}$ $^1\text{H}(J_{\text{H-H}})$ $^1\text{H}$ $\nu_{\text{as-NH}_2}$ $A_{1640}$	$\text{XC}_6\text{H}_4\text{F}$ ( $\text{CDCl}_3$ or $\text{CD}_3\text{CN}$ ) $\text{XC}_6\text{H}_5$ ( $\text{CDCl}_3$ ) $\text{XCH=CH}_2$ $\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO) $\text{XC}_6\text{H}_4\text{NH}_2$ ( $\text{CCl}_4$ ) $\text{XCH=CH}_2$ ( $\text{CCl}_4$ )	<i>d</i> <i>b</i> <i>f</i> <i>c</i> <i>c</i> <i>a</i>
	0.48 0.532	-0.35 -0.10 -0.101		0.40 0.48	$^{13}\text{C}$ $^1\text{H}$ $\nu_{\text{as-NH}_2}$ $^{19}\text{F}$	$\text{XC}_6\text{H}_5$ ( $\text{CDCl}_3$ ) $\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO) $\text{XC}_6\text{H}_4\text{NH}_2$ ( $\text{CCl}_4$ ) $\text{XC}_6\text{H}_4\text{F}$ ( $\text{CDCl}_3$ or $\text{CD}_3\text{CN}$ )	<i>b</i> <i>c</i> <i>c</i> <i>d</i>
	0.534	-0.30 -0.124		0.365 0.44	$^1\text{H}$ $\nu_{\text{as-NH}_2}$ $A_{1640}$ $^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO) $\text{XC}_6\text{H}_4\text{NH}_2$ ( $\text{CCl}_4$ ) $\text{XCH=CH}_2$ ( $\text{CCl}_4$ ) $\text{XC}_6\text{H}_4\text{F}$ ( $\text{CDCl}_3$ or $\text{CD}_3\text{CN}$ )	<i>c</i> <i>c</i> <i>a</i> <i>d</i>
	0.660	-0.103		0.33	$^{19}\text{F}$ $^1\text{H}$	$\text{XC}_6\text{H}_4\text{F}$ ( $\text{CDCl}_3$ or $\text{CD}_3\text{CN}$ ) $\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO)	<i>d</i> <i>c</i>
	0.44	-0.075		0.355 0.36	$^{13}\text{C}$ $^1\text{H}$ $\nu_{\text{as-NH}_2}$	$\text{XC}_6\text{H}_5$ ( $\text{CDCl}_3$ ) $\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO) $\text{XC}_6\text{H}_4\text{NH}_2$ ( $\text{CCl}_4$ )	<i>b</i> <i>c</i> <i>c</i>
			0.64 0.68	0.57 0.44 (0.76)	$\text{pK}_a$	$\text{XC}_6\text{H}_4$ -5-tetrazole (aq. DMSO) $\text{XC}_6\text{H}_4$ -5-tetrazole (KBr)	<i>h</i> <i>i</i>

TABLE XI (continued)

Group X	$\sigma_I$ ( $\sigma^*$ )	$\sigma_R$ ( $\sigma_R$ )	$\sigma_m$	$\sigma_p$	Method	Structural series (solvent)	Footnotes
			0.50 (0.30)	0.44	$\lambda_{\max}$	XC <sub>6</sub> H <sub>4</sub> -5-tetrazole (MeOH)	<i>j</i>
	0.45 (2.82)		0.46		p <i>K</i> <sub>a</sub>	5-X-tetrazole (aq.)	<i>k</i>
		(-0.14)		0.31	p <i>K</i> <sub>BH<sup>+</sup></sub>	5-X-tetrazole (aq.)	<i>k</i>
	0.12 (0.76)		0.09		p <i>K</i> <sub>a</sub>	5-X-tetrazole (aq.)	<i>k</i>
				1.02	p <i>K</i> <sub>BH<sup>+</sup></sub>	5-X-tetrazole (aq.)	<i>k</i>
	0.69 0.65 0.57 0.54	-0.11  (-0.03) -0.04	  0.60 0.52	  0.57 0.50	<sup>13</sup> C p <i>K</i> <sub>a</sub> p <i>K</i> <sub>a</sub> <sup>19</sup> F	XC <sub>6</sub> H <sub>5</sub> (CDCl <sub>3</sub> ) XCH <sub>2</sub> COOH (aq. EtOH) XC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub> (aq.) XC <sub>6</sub> H <sub>4</sub> F (MeCN)	<i>b</i> <i>m</i> <i>n, o</i> <i>n, o</i>
				0.52	<sup>1</sup> H	XC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub> (DMSO)	<i>c</i>
				0.71	$\nu_{as-NH_2}$	XC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub> (CCl <sub>4</sub> )	<i>c</i>
	0.62				p <i>K</i> <sub>a</sub>	XCH <sub>2</sub> COOH (aq. EtOH)	<i>m</i>
				0.59	<sup>1</sup> H	XC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub> (DMSO)	<i>c</i>
				0.62	$\nu_{as-NH_2}$	XC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub> (CCl <sub>4</sub> )	<i>c</i>

<sup>a</sup> (80IZV1562).<sup>b</sup> (80AJC1763).<sup>c</sup> (74JCS(P2)449).<sup>d</sup> (81JCR(S)364).<sup>e</sup> (81MI1).<sup>f</sup> (81T929).<sup>g</sup>  $\sigma_0 = 0.24$  (80MI2);  $\mathcal{F} = 1.17$ ,  $\mathcal{R} = -0.13$  (79JCS(P2)1670);  $\mathcal{F} = 1.02$ ,  $\mathcal{R} = -0.04$  (79OMR631).<sup>h</sup> (79JCS(P2)1670).<sup>i</sup> (80MI14).<sup>j</sup> (80MI3).<sup>k</sup> (83KGS1130).<sup>l</sup>  $\mathcal{F}$ , 0.52;  $\mathcal{R}$ , 0.02 (73JMC1207).<sup>m</sup> (82KGS264).<sup>n</sup> (67JOC3580).<sup>o</sup> (67MI2).

spectroscopy (79JCS(P2)1670; 80MI3; 80MI4). The discrepancy in the values of  $\sigma_m$  and  $\sigma_p$  constants for the 5-tetrazolyl group is accounted for by the application of different solvents.

To determine the  $\sigma_p$  constants for the *N*-azolyl groups, Elguero *et al.* used IR and PMR spectroscopy [Eqs. (23) and (24)] (74JCS(P2)449). In most cases, however, the  $\sigma_p$  constants obtained from the data on IR spectroscopy proved to be overestimated, which the authors attribute to the formation of azolylaniline associates. The  $\sigma_p$  constant for the 1-tetrazolyl group (0.52) estimated from the PMR data (74JCS(P2)449) agrees well with constants found from the  $pK_a$  of *p*-tetrazolylaniline in water (0.57) and from the  $^{19}\text{F}$ -NMR data of *p*-(tetrazolyl)fluorobenzene (0.50) (67JOC3580; 67MI2).

To determine the  $\sigma_I$  and  $\sigma_R^\circ$  constants for the *N*-azolyl groups, Fong used Eqs. (21) and (22) (80AJC1763); Elguero *et al.* used  $^{19}\text{F}$  NMR (81JCR(S)364). Using the intensities of the band  $\text{C}=\text{C}$  ( $A_{1640}$ ) in the IR spectra (series 20,  $\text{X} = \text{N}$ -azolyl groups), Frolov *et al.* used the Katritzky equation (70JA6861) to calculate the  $\sigma_R^\circ$  constants for some *N*-azolyl groups (80IZV1562) (Table XI).

Using Charton's equation [Eq. (25)] for substituted acetic acids

$$\sigma_I = -0.251pK_a + 1.186 \quad (25)$$

(64JOC1222) Poplavskii *et al.* calculated the  $\sigma_I$  constants for tetrazolyl groups from the  $pK_a$  values of the corresponding tetrazolylacetic acids (82KGS264).

As seen from Table XI the values of the  $\sigma_I$  constants for the 1-tetrazolyl group found by various methods agree fairly well.

According to Fong the increase in the inductive effects of *N*-azolyl groups in the sequence shown in Fig. 2 is closely connected with the concept of group electronegativity (80AJC1763). This sequence has been observed in the

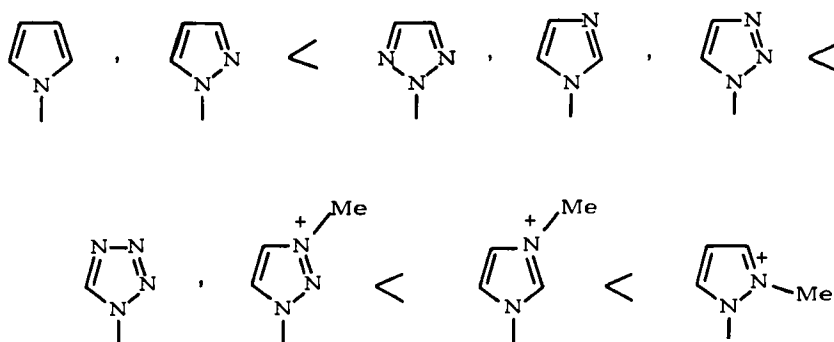


FIG. 2. Sequence of increase of inductive effects in *N*-azolyl groups.

changes of NH acidity of five-membered heterocycles: pyrrole ( $pK_a$  23.3), pyrazole (20.4), imidazole (18.9), tetrazole (4.89) (83KGS369).

### III. Electronic Effects of Substituted Heteroaromatic Groups

#### A. SIX-MEMBERED HETEROAROMATIC GROUPS

Electronic effects of substituted six-membered heteroaromatic groups have been little studied.

As for those with one heteroatom, there are data available only on the 2,6-diphenyl-4-pyridyl group, on its charged forms, and some substituted pyridinio groups (Table XIV). But the bulk concerns the substituted pyrimidinyl and s-triazinyl groups. This section also contains evidence on some fused and other heterocyclic groups.

##### 1. *Substituted Pyrimidinyl Groups*

The  $\sigma$  constants for pyrimidinyl groups were determined by the NMR method from the values of the  $^{13}\text{C}$  shift of meta and para carbon atoms of the benzene ring in the spectra of substituted phenylpyrimidines (series 8). For some substituted pyrimidinyl groups the constants were also determined by  $^{19}\text{F}$  NMR from the shifts of meta and para fluorine atoms in the spectra of fluorophenylpyrimidines (series 9). Either method makes it possible to determine only inductive and mesomeric constants for substituted groups using Eqs. (10)–(13). Using the two methods separately to determine these constants enables one to judge more confidently the reliability of the values (Table XII).

In the  $^{13}\text{C}$ -NMR method, the effect of diamagnetic anisotropy of the pyrimidinyl groups (the influence of induced ring current) on the screening of benzene ring carbon atoms must be considered by introducing anisotropic corrections (83IZV299). These corrections were the same as those for the phenyl group. For substituted phenyl, pyrimidinyl, etc. groups the corrections may, in principle, vary depending on the electronic properties of the substituents. In the framework of the approximation under discussion it was assumed admissible, however, to use certain averaged corrections, just as for the unsubstituted pyrimidinyl groups. Application of corrections results in a slight admixture of  $^{13}\text{C}$  signals into the high field, so the calculated values of inductive constants for electron-withdrawing pyrimidinyl groups decrease by about 0.03–0.05 and agree more closely with those obtained from the  $^{19}\text{F}$ -NMR spectra. The mesomeric constants remain practically unchanged.



TABLE XII  
 $\sigma$  VALUES FOR SUBSTITUTED PYRIMIDINYL GROUPS

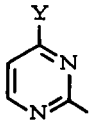
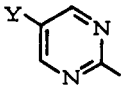
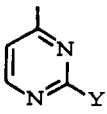
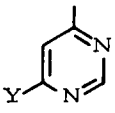
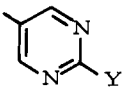
Group X	Substituent Y	$\sigma_1$	$\sigma_R^\circ$	Method	Structural series (solvent)	Footnotes
	Me	-0.02	0.09	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ ( $\text{CCl}_4$ )	<i>a</i>
		0.08	0.08	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (DMSO)	<i>a</i>
	Ph	0.03	0.10	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ ( $\text{CCl}_4$ )	<i>a</i>
		0.13	0.09	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (DMSO)	<i>a</i>
	F	0.19	0.13	$^{13}\text{C}$	XPh (acetone)	<i>b</i>
		0.19	0.12	$^{13}\text{C}$	XPh (DMSO)	<i>b</i>
	Cl	0.16	0.13	$^{13}\text{C}$	XPh (acetone)	<i>b</i>
		0.17	0.12	$^{13}\text{C}$	XPh (DMSO)	<i>b</i>
		0.09	0.13	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ ( $\text{CCl}_4$ )	<i>a</i>
		0.15	0.12	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (DMSO)	<i>a</i>
	Br	0.09	0.14	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ ( $\text{CCl}_4$ )	<i>a</i>
		0.14	0.13	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (DMSO)	<i>a</i>
	OMe	0.05	0.11	$^{13}\text{C}$	XPh (acetone)	<i>b</i>
		0.08	0.10	$^{13}\text{C}$	XPh (DMSO)	<i>b</i>
		-0.02	0.11	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ ( $\text{CCl}_4$ )	<i>a</i>
		0.08	0.09	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (DMSO)	<i>a</i>
	NMe <sub>2</sub>	-0.05	0.09	$^{13}\text{C}$	XPh (acetone)	<i>b</i>
		0.00	0.08	$^{13}\text{C}$	XPh (DMSO)	<i>b</i>
		-0.08	0.07	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ ( $\text{CCl}_4$ )	<i>a</i>
		0.02	0.06	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (DMSO)	<i>a</i>
	CN	0.23	0.13	$^{13}\text{C}$	XPh (acetone)	<i>b</i>
		0.22	0.12	$^{13}\text{C}$	XPh (DMSO)	<i>b</i>
		0.20	0.15	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ ( $\text{CCl}_4$ )	<i>a</i>
		0.21	0.12	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (DMSO)	<i>a</i>
	Cl	0.07	0.11	$^{13}\text{C}$	XPh (acetone)	<i>c</i>
	OMe	0.00	0.07	$^{13}\text{C}$	XPh (acetone)	<i>c</i>
	NH <sub>2</sub>	-0.04	0.06	$^{13}\text{C}$	XPh (acetone)	<i>c</i>
	COOEt	0.11	0.14	$^{13}\text{C}$	XPh (acetone)	<i>c</i>
	CN	0.16	0.16	$^{13}\text{C}$	XPh (acetone)	<i>c</i>
	Me	0.16	0.07	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ ( $\text{CCl}_4$ )	<i>d</i>
		0.15	0.08	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (DMSO)	<i>d</i>
	F	0.32	0.12	$^{13}\text{C}$	XPh (acetone)	<i>b</i>
		0.30	0.12	$^{13}\text{C}$	XPh (DMSO)	<i>b</i>
	Cl	0.30	0.14	$^{13}\text{C}$	XPh (acetone)	<i>b</i>
		0.31	0.11	$^{13}\text{C}$	XPh (DMSO)	<i>b</i>
		0.33	0.12	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ ( $\text{CCl}_4$ )	<i>d</i>
		0.24	0.13	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (DMSO)	<i>d</i>
	Br	0.34	0.12	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ ( $\text{CCl}_4$ )	<i>d</i>
		0.24	0.13	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (DMSO)	<i>d</i>
	OMe	0.24	0.09	$^{13}\text{C}$	XPh (acetone)	<i>b</i>
		0.25	0.09	$^{13}\text{C}$	XPh (DMSO)	<i>b</i>
		0.25	0.09	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ ( $\text{CCl}_4$ )	<i>d</i>
		0.22	0.10	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (DMSO)	<i>d</i>

TABLE XII (continued)

Group X	Substituent Y	$\sigma_1$	$\sigma_R$	Method	Structural series (solvent)	Footnotes
	NMe <sub>2</sub>	0.13	0.08	<sup>13</sup> C	XPh (acetone)	<i>b</i>
		0.12	0.08	<sup>13</sup> C	XPh (DMSO)	<i>b</i>
		0.18	0.06	<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (CCl <sub>4</sub> )	<i>d</i>
		0.14	0.07	<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (DMSO)	<i>d</i>
	CN	0.39	0.12	<sup>13</sup> C	XPh (acetone)	<i>b</i>
		0.34	0.12	<sup>13</sup> C	XPh (DMSO)	<i>b</i>
		0.38	0.12	<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (CCl <sub>4</sub> )	<i>d</i>
		0.26	0.14	<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (DMSO)	<i>d</i>
	Me	0.22	0.07	<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (CCl <sub>4</sub> )	<i>d</i>
		0.18	0.08	<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (DMSO)	<i>d</i>
	F	0.28	0.11	<sup>13</sup> C	XPh (acetone)	<i>b</i>
		0.25	0.11	<sup>13</sup> C	XPh (DMSO)	<i>b</i>
	Cl	0.28	0.11	<sup>13</sup> C	XPh (acetone)	<i>b</i>
		0.25	0.11	<sup>13</sup> C	XPh (DMSO)	<i>b</i>
		0.30	0.11	<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (CCl <sub>4</sub> )	<i>d</i>
		0.20	0.12	<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (DMSO)	<i>d</i>
	Br	0.32	0.11	<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (CCl <sub>4</sub> )	<i>d</i>
		0.22	0.12	<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (DMSO)	<i>d</i>
	OMe	0.20	0.08	<sup>13</sup> C	XPh (acetone)	<i>b</i>
		0.16	0.08	<sup>13</sup> C	XPh (DMSO)	<i>b</i>
		0.20	0.06	<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (CCl <sub>4</sub> )	<i>d</i>
		0.15	0.08	<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (DMSO)	<i>d</i>
	NMe <sub>2</sub>	-0.09	0.06	<sup>13</sup> C	XPh (acetone)	<i>b</i>
		0.11	0.06	<sup>13</sup> C	XPh (DMSO)	<i>b</i>
		0.12	0.04	<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (CCl <sub>4</sub> )	<i>d</i>
		0.09	0.05	<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (DMSO)	<i>d</i>
	CN	-0.39	0.12	<sup>13</sup> C	XPh (acetone)	<i>b</i>
		0.33	0.12	<sup>13</sup> C	XPh (DMSO)	<i>b</i>
		0.41	0.14	<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (CCl <sub>4</sub> )	<i>d</i>
		0.28	0.14	<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (DMSO)	<i>d</i>
	Cl	0.32	-0.03	<sup>13</sup> C	XPh (acetone)	<i>c</i>
	OMe	0.24	-0.06	<sup>13</sup> C	XPh (acetone)	<i>c</i>
	NH <sub>2</sub>	0.21	-0.09	<sup>13</sup> C	XPh (acetone)	<i>c</i>
	NMe <sub>2</sub>	0.19	-0.09	<sup>13</sup> C	XPh (acetone)	<i>c</i>
	COOEt	0.36	-0.01	<sup>13</sup> C	XPh (acetone)	<i>c</i>
	CN	0.40	-0.01	<sup>13</sup> C	XPh (acetone)	<i>c</i>

<sup>a</sup> (80IZV1781).<sup>b</sup> (82MI1).<sup>c</sup> (83IZV299).<sup>d</sup> (83MI1).

Attempts to calculate anisotropic corrections more accurately can hardly justify the effort, bearing in mind that the other factors (medium, concentration, temperature, detection technique), combined with the errors due to the calculation equations used, cause a similar dispersion of values.

A comparison of the  $\sigma_1$  values (Table XII) obtained by using  $\text{CCl}_4$  and acetone or DMSO as solvents illustrates the strong influence of the medium on the value of the inductive effect of substituted pyrimidinyl groups. The best agreement between the  $\sigma_1$  values has been noted for solvents of the same type, such as acetone and DMSO (82MI1).

The listed values of the inductive and mesomeric constants for 4- and 5-substituted 2-pyrimidinyl groups, and 2- and 6-substituted 4-pyrimidinyl groups, point, on the whole, to their electron-withdrawing character. This character grows stronger when electron-withdrawing substituents (CN, COOEt) are introduced into the pyrimidine ring but grows weaker when the ring acquires electron-releasing substituents (OMe,  $\text{NH}_2$ , and particularly  $\text{NMe}_2$ ). The 2-substituted 5-pyrimidinyl groups that have been studied are, by their inductive effect, electron-withdrawing substituents, and by their mesomeric effect they are weak electron donors, except for the 2-cyano-5-pyrimidinyl group (83IZV299). The dependence of inductive and mesomeric constants for substituted pyrimidinyl groups on the electronic nature of the substituents in the pyrimidine ring can be expressed in a numerical form (Section IV,A,2).

## 2. Substituted *s*-Triazinyl Groups

A wide variety of numerical data characterize the electronic effects of some 4,6-disubstituted *s*-triazinyl groups. The  $\sigma$  constants for these groups listed in Table XIII have been determined from  $^{13}\text{C}$  spectra of phenyl-*s*-triazines (series 8) (83TH1) and the PMR spectra and  $\text{pK}_a$  of *p*-hydroxyphenyl-*s*-triazines (series 12) (74BCJ1301).

The  $\sigma$  constants for the 4,6-dimethyl-*s*-triazinyl group were evaluated by two independent methods: (1) from the  $\text{pK}_a$  values of *m*- and *p*-(4,6-dimethyl-2-triazinyl)benzoic acids (series 10) and (2) from the  $^{19}\text{F}$  spectra of 4,6-dimethyl-2-(*m*-/*p*-fluorophenyl)triazines (series 9) in various solvents (74JOC2591). That the  $\sigma_1$  values in alcoholic media and in DMSO are very close can be accounted for by the low protophilicity of heterocyclic nitrogen atoms of the triazine ring and by their small steric accessibility in the presence of two methyl groups in the ring. At the same time, the polarity of the medium exerts an appreciable effect on the value of the inductive constants (see Table XIII).

TABLE XIII  
 $\sigma$  VALUES FOR 4(6)-SUBSTITUTED 2-S-TRIAZINYL GROUPS

Substituents in triazine ring		$\sigma_1$	$\sigma_R^\circ$ ( $\sigma_R$ )	$\sigma_p^-$ ( $\sigma_p$ )	Method	Structural series (solvent)	Footnotes
$Y^1$	$Y^2$						
H	OMe	0.15	0.20		$^{13}\text{C}$	XPh (acetone)	<i>a</i>
Me	Me	0.15	(0.24)	(0.39)	$pK_a$	$\text{XC}_6\text{H}_4\text{COOH}$ (aq·EtOH)	<i>b, c</i>
		0.18	0.19		$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (MeOH)	<i>c</i>
		0.08	0.18		$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ ( $\text{CCl}_4$ )	<i>c</i>
		0.16	0.18		$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ (DMSO)	<i>c</i>
Cl	Cl	0.32	0.24		$^{13}\text{C}$	XPh (acetone)	<i>a</i>
				0.82	$pK_a$	$\text{XC}_6\text{H}_4\text{OH}$ (aq.)	<i>d, e</i>
				0.88	$^1\text{H}$	$\text{XC}_6\text{H}_4\text{OH}$ (DMSO)	<i>f, e</i>
Cl	OMe	0.18	0.22		$^{13}\text{C}$	XPh (acetone)	<i>a</i>
Cl	NMe <sub>2</sub>	0.13	0.22		$^{13}\text{C}$	XPh (acetone)	<i>a</i>
OMe	OMe			0.66	$pK_a$	$\text{XC}_6\text{H}_4\text{OH}$ (aq.)	<i>e</i>
				0.70	$^1\text{H}$	$\text{XC}_6\text{H}_4\text{OH}$ (DMSO)	<i>e</i>
OMe	OPh			0.71	$pK_a$	$\text{XC}_6\text{H}_4\text{OH}$ (aq.)	<i>e</i>
				0.75	$^1\text{H}$	$\text{XC}_6\text{H}_4\text{OH}$ (DMSO)	<i>e</i>
OMe	NMe <sub>2</sub>			0.57	$pK_a$	$\text{XC}_6\text{H}_4\text{OH}$ (aq.)	<i>e</i>
				0.59	$^1\text{H}$	$\text{XC}_6\text{H}_4\text{OH}$ (DMSO)	<i>e</i>
OPh	OPh			0.80	$^1\text{H}$	$\text{XC}_6\text{H}_4\text{OH}$ (DMSO)	<i>e</i>
OPh	NMe <sub>2</sub>			0.61	$pK_a$	$\text{XC}_6\text{H}_4\text{OH}$ (aq.)	<i>e</i>
				0.63	$^1\text{H}$	$\text{XC}_6\text{H}_4\text{OH}$ (DMSO)	<i>e</i>
NMe <sub>2</sub>	NMe <sub>2</sub>			0.47	$pK_a$	$\text{XC}_6\text{H}_4\text{OH}$ (aq.)	<i>e</i>
				0.47	$^1\text{H}$	$\text{XC}_6\text{H}_4\text{OH}$ (DMSO)	<i>e</i>

<sup>a</sup> (83TH1).<sup>b</sup>  $\sigma_m$ , 0.25.<sup>c</sup> (74JOC2591).<sup>d</sup> Calculated from Eq. (26).<sup>e</sup> (74BCJ1301).<sup>f</sup> Calculated from Eq. (27).

The  $\sigma_p^-$  constants for some disubstituted triazinyl groups with electron-releasing substituents  $Y^1$  and  $Y^2$  have been determined from the values of  $pK_a$  and the OH chemical shifts in (*p*-hydroxyphenyl)triazines (**13**) (74BCJ1301). The  $\sigma_p^-$  constants for substituted triazinyl groups have been found to correlate with the  $\sigma_m$  constants for the  $Y^1$  and  $Y^2$  substituents [Eqs. (26) and (27), respectively]. These equations were used to calculate the  $\sigma_p^-$  constants for the unsubstituted and 4,6-dichloro-2-triazinyl groups. Since Eqs. (26) and (27) have been obtained by treating the data on triazinyl

groups with substituents only of the +M, -I type, the calculated  $\sigma_p^-$  values for the dichlorotriazinyl group can be assumed to estimate correctly its resonance effect. However, the  $\sigma_p^-$  value for the unsubstituted *s*-triazinyl group

$$\sigma_p^- = 0.30 \Sigma \sigma_m(Y) + 0.60 \quad (26)$$

$$\sigma_p^- = 0.35 \Sigma \sigma_m(Y) + 0.62 \quad (27)$$

may not coincide with the values of the free terms in Eqs. (26) and (27).

### 3. Other Six-Membered Heteroaromatic Groups

A fused benzene has little influence on the electronic effects of azinyl groups. This can be concluded by comparing the values of the inductive and mesomeric constants for the 2-quinolyl ( $\sigma_I = 0.13$ ,  $\sigma_R^\circ = 0.01$ ) and 2-pyridyl (0.10 and 0.01) groups, as well as for the 2-quinazolinyl (0.06 and 0.10) and 2-pyrimidinyl (0.05 and 0.10) groups determined under identical conditions (85MI4). A similar situation has been noted for the respective 4-substituted 2-quinazolinyl, and 4-substituted 2-pyrimidinyl groups. The values of these constants were determined from  $^{13}\text{C}$  spectra of the respective phenyl heterocycles (series 8) (Table XIV).

From the  $^{19}\text{F}$  chemical shifts of *m*- and *p*-fluorophenyl derivatives of perimidine (21–25), the  $\sigma_I$  and  $\sigma_R$  constants have been calculated for two uncharged (21, 22) and three cationic 2-perimidinyl groups (23–25). The para fluorine atom has been assumed to be polar conjugated with the perimidine system, which leads to the summation, in the  $\sigma_R$  constant, of two effects: mesomeric and polar conjugation (81TH1). On the whole, the electron-withdrawing ability of the neutral 2-perimidinyl group is comparable to that of substituents such as halogens, but a charged 2-perimidinyl group exceeds in this respect even a nitro group.

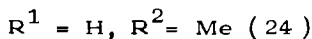
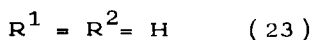
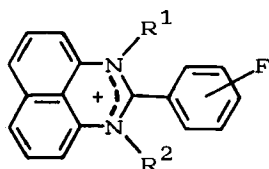
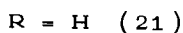
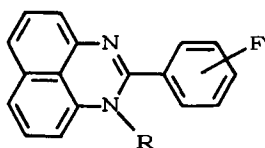
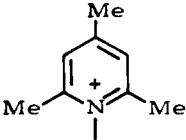
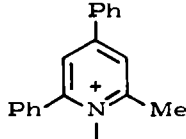
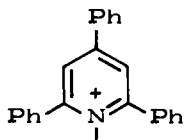
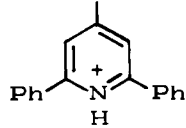
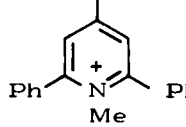
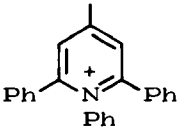
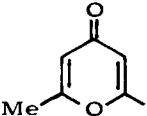
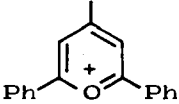
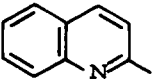
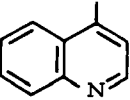
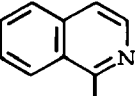


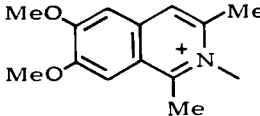
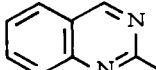
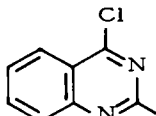
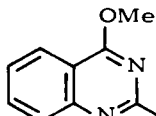
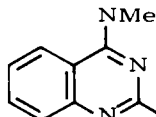
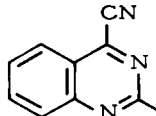
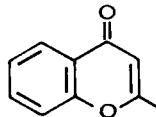
TABLE XIV  
 $\sigma$  VALUES FOR OTHER SIX-MEMBERED HETEROAROMATIC GROUPS

Group X	$\sigma_I$ ( $\sigma^*$ )	$\sigma_R^+$ ( $\sigma_R$ )	$\sigma_m$	$\sigma_p$	Method	Structural series (solvent)	Footnotes
	0.67	-0.09	0.69	0.71	$pK_a$	$XC_6H_4NH_3^+$ (MeCN)	<i>a</i>
			0.62	0.58	$^1H$	$XC_6H_4NH_2$ (DMSO)	<i>b</i>
					$^{13}C$	XPh (DMSO)	<i>b</i>
					$^{19}F$	$XC_6H_4F$ (DMSO)	<i>b</i>
			0.65	0.70	$pK_a$	$XC_6H_4NH_3^+$ (MeCN)	<i>a</i>
	0.36	-0.03	0.63	0.71	$pK_a$	$XC_6H_4NH_3^+$ (MeCN)	<i>a</i>
			0.34	0.33	$^1H$	$XC_6H_4NH_2$ (DMSO)	<i>b</i>
					$^{13}C$	XPh (DMSO)	<i>b</i>
					$^{19}F$	$XC_6H_4F$ (DMSO)	<i>b</i>
				0.72	$pK_a$	$XC_6H_4NH_3^+$ (MeCN)	<i>c</i>
				0.70	$pK_a$	$XC_6H_4NH_3^+$ (MeCN)	<i>c</i>

(continued)

TABLE XIV (continued)

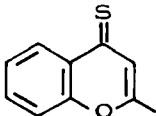
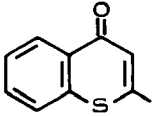
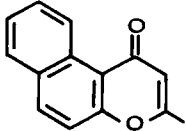
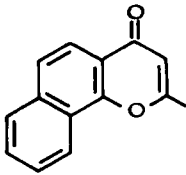
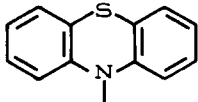
Group X	$\sigma_I$ ( $\sigma^*$ )	$\sigma_R^\circ$ ( $\sigma_R$ )	$\sigma_m$	$\sigma_p$	Method	Structural series (solvent)	Footnotes
				0.74	$pK_a$	$XC_6H_4\overset{+}{N}H_3$ (MeCN)	<i>c</i>
	0.33	(0.10)	0.381	0.434	$pK_a$	$XC_6H_4COOH$ (aq. methyl Cellosolve <sup>®</sup> )	<i>d</i>
	0.29	0.10			$^{19}F$	$XC_6H_4F$ ( $C_2H_4Cl_2$ )	<i>d</i>
			0.38	0.43	$\Delta\lambda_{max}$	$XC_6H_4N=NC_6H_4\overset{+}{N}HMe_2$ (aq. $H_2SO_4$ )	<i>d</i>
38 				1.17	$pK_a$	$XC_6H_4\overset{+}{N}H_3$ (MeCN)	<i>c</i>
	(1.15)				$E_{1/2}$	$X(CH=CH)_nPh$ (aq. EtOH)	<i>e</i>
	(1.23)				$pK_a$	$XCH=\overset{+}{N}HNHC(NH_2)=NPh$ (aq.)	<i>f</i>
	0.13	0.01			$^{19}F$	$XC_6H_4F$ ( $CH_2Cl_2$ )	<i>g</i>
	(1.22)				$E_{1/2}$	$XCH=CHPy$ (aq. EtOH)	<i>h</i>
	(1.19)				$E_{1/2}$	$XCH=CHPy$ (aq. EtOH)	<i>e</i>

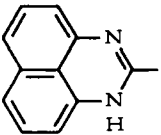
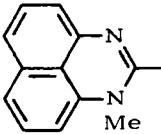
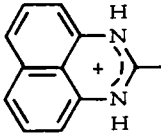
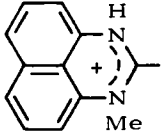
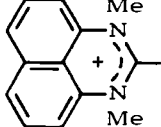
39				0.65	0.66	pK <sub>a</sub>	XC <sub>6</sub> H <sub>4</sub> NH <sub>3</sub> <sup>+</sup> (MeCN)	<i>a</i>
		0.06	0.10			<sup>13</sup> C	XPh (acetone)	<i>i</i>
		0.14	0.12			<sup>13</sup> C	XPh (acetone)	<i>i</i>
		0.01	0.11			<sup>13</sup> C	XPh (acetone)	<i>i</i>
		-0.08	0.09			<sup>13</sup> C	XPh (acetone)	<i>i</i>
		0.19	0.12			<sup>13</sup> C	XPh (acetone)	<i>i</i>
		0.400	(0.01)	0.405	0.399	pK <sub>a</sub>	XC <sub>6</sub> H <sub>4</sub> COOH (aq. methyl Cellosolve <sup>®</sup> )	<i>d</i>
		0.31	0.12	0.372	0.697	pK <sub>a</sub>	XC <sub>6</sub> H <sub>4</sub> NH <sub>3</sub> <sup>+</sup> (aq. EtOH)	<i>j</i>
						<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (C <sub>2</sub> H <sub>4</sub> Cl <sub>2</sub> )	<i>d</i>
				0.39	0.42	Δλ <sub>max</sub>	XC <sub>6</sub> H <sub>4</sub> N=NC <sub>6</sub> H <sub>4</sub> NHMe <sub>2</sub> <sup>+</sup> (aq. H <sub>2</sub> SO <sub>4</sub> )	<i>d</i>

(continued)



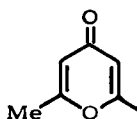
TABLE XIV (continued)

Group X	$\sigma_1$ ( $\sigma^*$ )	$\sigma_R^\circ$ ( $\sigma_R$ )	$\sigma_m$	$\sigma_p$	Method	Structural series (solvent)	Footnotes
	0.33	(0.02)	0.345	0.351	$pK_a$	$XC_6H_4COOH$ (aq. methyl Cellosolve®)	<i>d</i>
	0.36	0.06	0.48		$pK_a$	$XC_6H_4COOH$ (aq. methyl Cellosolve®)	<i>d</i>
					$^{19}F$	$XC_6H_4F$ ( $C_2H_4Cl_2$ )	<i>d</i>
			0.40	0.45	$\Delta\lambda_{max}$	$XC_6H_4N=NC_6H_4\dot{N}HMe_2$	<i>d</i>
	0.377		0.381	0.375	$pK_a$	$XC_6H_4COOH$ (aq. methyl Cellosolve®)	<i>j</i>
				0.586	$pK_a$	$XC_6H_4\dot{N}H_3$ (aq. EtOH)	<i>j</i>
	0.364		0.365	0.378	$pK_a$	$XC_6H_4COOH$ (aq. methyl Cellosolve®)	<i>j</i>
	0.23 (1.42)				$pK_a$	$XCH_2COOH$ (aq. EtOH)	<i>k</i>

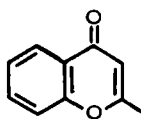
	0.24	0.10	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$	<i>l</i>
	0.19	0.04	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$	<i>l</i>
	0.31	(0.25)	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$	<i>l</i>
	0.42	(0.15)	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$	<i>l</i>
	0.68	(0.09)	$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$	<i>l</i>

<sup>a</sup> (74KGS1349).<sup>b</sup> (81CCC584).<sup>c</sup> (76KGS1025).<sup>d</sup> (73ZOB636).<sup>e</sup> (69MI1).<sup>f</sup> (85PHA356).<sup>g</sup> (76ZOB162).<sup>h</sup> (70MI3).<sup>i</sup> (85MI4).<sup>j</sup> (68ZOB1139).<sup>k</sup> (83KGS369).<sup>l</sup> (81TH1).

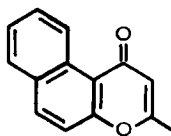
Other cationic substituents such as substituted N-protonated pyridyl and especially pyrylium-4-yl are highly electron-withdrawing groups. But substituted pyridinio groups develop even a higher electron-withdrawing capacity, and judging by the values of the  $\sigma_m$  and  $\sigma_p$  constants, it decreases in the presence of methyl substituents in the heterocycle and increases in the presence of phenyl substituents (81CCC584). For the 2,4,6-triphenylpyridinio group, essentially different values are listed. The low values estimated by the NMR method appear to be due to the influence of the magnetic anisotropy of phenyl groups.



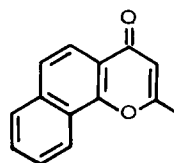
( 26 )



( 27 )



( 28 )



( 29 )

Data on such groups as 2-pyrone (26), chromone (27), and benzochromone (28) and (29) can be placed among heteroaromatic substituents only with reserve. Their structure suggests comparing them with ester groups. Indeed, the values of the Hammett  $\sigma_m$  and  $\sigma_p$  constants for these groups (Table XIV) are close to those for the  $\text{COOCH}_3$  group ( $\sigma_m$  0.36,  $\sigma_p$  0.45) (79MI1). The higher values of the inductive constants for the 2-pyrone and 2-chromonyl groups found from  $\text{p}K_a$  values as compared to those determined from  $^{19}\text{F}$  shifts are due to the effects of specific solvation (73ZOB636).

## B. ELECTRONIC EFFECTS OF SUBSTITUTED FIVE-MEMBERED HETEROAROMATIC GROUPS

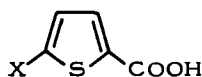
The available data characterizing quantitatively the electronic effects of substituted five-membered heteroaromatic groups can be summarized as follows.

1. For the series of substituted five-membered heteroaromatic groups with one heteroatom in the ring there are  $\sigma_m$  and  $\sigma_p$  constants for 5-substituted 2-thienyl, 2-selenienyl, 2-furyl, and some substituted *N*-pyrrolyl groups.
2. For the series of substituted five-membered heteroaromatic groups with two and more heteroatoms in the ring the  $\sigma$  constants are known for quite a number of substituted *N*-azolyl groups and there are comparatively few data for substituted five-membered C-heteroaromatic groups with two and more heteroatoms in the ring.

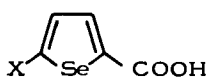
1. *Containing One Heteroatom*

Table XV gives values of the  $\sigma_p$  constants for 5-substituted 2-thienyl and 2-selenienyl groups (70G777), the  $\sigma^*$  constants for the 5-substituted 2-thienyl groups (65RTC1169), as well as the  $\sigma_m$  and  $\sigma_p$  constants for 5-substituted 2-furyl groups (74CCC1711; 77CCC105).

Dell'erba *et al.* calculated the  $\sigma_p$  constants for 5-substituted 2-thienyl and 2-selenienyl groups by using the dependence between the constants of ionization of the corresponding 2-substituted hetaryl-5-carboxylic acids in aqueous butyl Cellosolve<sup>®</sup> with the  $\sigma_p$  constants for the X substituent [for series **30**, Eq. (28); for series **31**, Eq. (29)] (70G777).



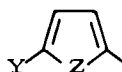
( 30 )



( 31 )

X = H, Me, Cl, Br, NO<sub>2</sub>

TABLE XV  
 $\sigma$  VALUES FOR SUBSTITUTED FIVE-MEMBERED HETEROAROMATIC GROUPS<sup>a</sup>



Substituent Y	Z = S		Z = Se	Z = O	
	$\sigma^{*a}$	$\sigma_p^b$	$\sigma_p^b$	$\sigma_m^c$	$\sigma_p^d$
Me	0.84	-0.03	-0.03	0.085	-0.17
Et		-0.02	-0.02	0.086	-0.16
Cl	1.26	0.13	0.13		
Br	1.29	0.12	0.12	0.15	-0.001
I		0.12	0.11		-0.03
CHO				0.22	-0.05
CH <sub>2</sub> OH					-0.12
Ac		0.19	0.18	0.24	0.08
CN				0.25	0.10
NO <sub>2</sub>	1.65	0.29	0.24		0.20

<sup>a</sup>  $\log k$  XCOOEt (aq. acetone) (65RTC1169).

<sup>b</sup>  $pK_a$  2-X-hetaryl-5-COOH (aq. butyl Cellosolve) (70G777).

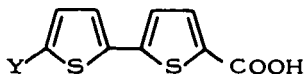
<sup>c</sup>  $pK_a$  XC<sub>5</sub>H<sub>4</sub>NH<sup>+</sup> (77CCC105).

<sup>d</sup>  $pK_a$  XC<sub>6</sub>H<sub>4</sub>COOH (aq. EtOH) (74CCC1711).

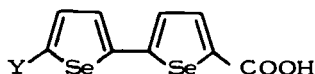
$$\text{p}K_{\text{a}} = 4.87 - 0.56\sigma_{\text{p}} \quad (28)$$

$$\text{p}K_{\text{a}} = 5.00 - 0.50\sigma_{\text{p}} \quad (29)$$

The 5-substituted 2-thienyl and 2-selenienyl groups were considered as the X substituent in **32** and **33**.



( 32 )



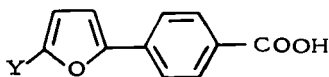
( 33 )

Y = Me, Et, Cl, Br, I, Ac, NO<sub>2</sub>

As seen from Table XV, the 5-substituted 2-thienyl and 2-selenienyl groups, except for the alkyl substituted, were found by the Italian authors to display an electron-withdrawing property roughly dependent on that of the Y substituent. By their total effect, the 5-alkyl-2-thienyl and -2-selenienyl groups are weak electron-releasing substituents.

From the data on acid- and base-catalyzed hydrolysis rates,  $\sigma^*$  values were derived for the 5-substituted 2-thienyl groups (65RTC1169).

To calculate the  $\sigma_{\text{p}}$  constants for 5-substituted 2-furyl groups Fišera *et al.* used the  $\text{p}K_{\text{a}}$  values of substituted benzoic acids (**34**) with 5-substituted 2-furyl



( 34 )

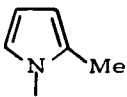
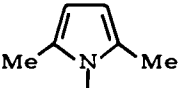
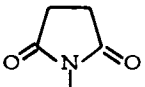
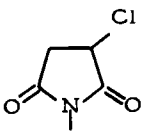
Y = Me, Et, Br, I, CHO, CH<sub>2</sub>OH, Ac, CN, NO<sub>2</sub>

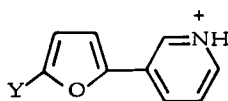
groups as substituents (74CCC1711). According to these authors, the furyl groups having substituents such as CHO, Br, and I display a weak electron-releasing character (see Table XV); but in the presence of strong electron-withdrawing substituents such as Ac and NO<sub>2</sub> groups, they display a weak electron-withdrawing property (74CCC1711).

The  $\sigma_{\text{m}}$  constants for 5-substituted 2-furyl groups have been estimated from the  $\text{p}K_{\text{a}}$  values for furylpyridinium cations (**35**) (77CCC105). Equation (30) was used to calculate the  $\sigma_{\text{m}}$  constants (64JCS3591).

$$\sigma_{\text{m}} = (\text{p}K_0 - \text{p}K)/6.01 \quad (30)$$

TABLE XVI  
 $\sigma$  VALUES FOR SUBSTITUTED *N*-PYRROLYL GROUPS

Group X	$\sigma_I$	$\sigma_R^\circ$ ( $\sigma_R$ )	$\sigma_m$	$\sigma_p$	Method	Structural series (solvent)	Footnotes
		-0.43			$A_{1640}$	$XCH=CH_2$ ( $CCl_4$ )	<i>a</i>
			0.49	0.38	$pK_a$	$XC_6H_4COOH$ (aq. EtOH)	<i>b</i>
	0.366	(-0.110)	0.339	0.313	$pK_a$	$XC_6H_4COOH$ (aq. EtOH)	<i>c</i>
	0.317	-0.073			$^{19}F$	$XC_6H_4F$ ( $C_2H_4Cl_2$ )	<i>c</i>
	0.489	(-0.032)	0.469	0.456	$pK_a$	$XC_6H_4COOH$ (aq. EtOH)	<i>c</i>
	0.387	-0.028			$^{19}F$	$XC_6H_4F$ ( $C_2H_4Cl_2$ )	<i>c</i>

<sup>a</sup> (80IZV1562).<sup>b</sup>  $\mathcal{F}$ , 0.52;  $\mathcal{R}$ , -0.10 (77JMC304)<sup>c</sup> (76KGS906).

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Y = Me, Et, Br, CHO, Ac, CN

There are also data on  $\sigma$  constants characterizing the electronic effects of some substituted *N*-pyrrolyl groups (Table XVI) (76KGS906; 77JMC304; 80IZV1562), but no data are available on the substituted *C*-pyrrolyl groups.

## 2. Containing Two or More Heteroatoms

Tables XVII and XVIII give the  $\sigma$  constants for substituted five-membered heteroaromatic groups with two or more heteroatoms in the ring.

TABLE XVII  
 $\sigma$  VALUES FOR SUBSTITUTED *N*-AZOLYL GROUPS<sup>a</sup>

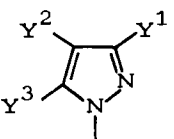
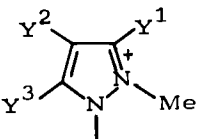
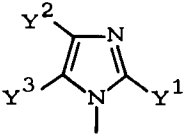
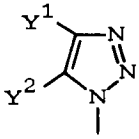
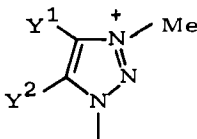
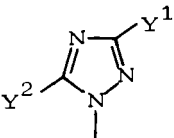
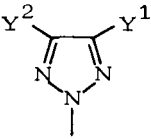
Group	Y <sup>1</sup>	Y <sup>2</sup>	Y <sup>3</sup>	$\sigma_1$	$\sigma_R^\circ$
	Cl	H	H	0.33	-0.155
	H	Cl	H	0.28	-0.14
	H	H	Cl	0.10	-0.02
	Cl	H	Cl	0.20	-0.03
	Br	H	H	0.33	-0.15
	H	Br	H	0.52	-0.045
	H	H	Br	0.15	-0.025
	Br	Br	H	0.51	-0.055
	Br	H	Br	0.19	-0.04
	H	Br	Br	0.21	-0.015
	Br	Br	Br	0.43	-0.02
	Me <sup>b</sup>	H	H	0.26	-0.165
	H	H	Me	0.01	-0.06
	Me <sup>c</sup>	H	Me	0.279 <sup>d</sup>	-0.113 <sup>d</sup>
	<i>t</i> -Bu <sup>e</sup>	H	<i>t</i> -Bu	0.155 <sup>d</sup>	-0.027 <sup>d</sup>
	H	H	H	1.11	-0.075
	H	H	Cl	0.34	-0.055
	H	Cl	H	0.91	-0.045
	SH	H	H	0.406 <sup>d</sup>	-0.070 <sup>d</sup>
	H	H	H	0.93	-0.155
	Cl	H		0.53	-0.10
	H	Cl		0.36	-0.04
	Me	H		0.37	-0.08
	H	Me		0.34	0.005
	H	SH		0.536 <sup>d</sup>	-0.095 <sup>d</sup>
	H	SMe		0.483 <sup>d</sup>	-0.043 <sup>d</sup>
	H	H		0.74	-0.055
	H	Me		0.81	-0.03
	Me	H		0.79	-0.06

TABLE XVII (continued)

Group	Y <sup>1</sup>	Y <sup>2</sup>	Y <sup>3</sup>	I	$\sigma_R^\circ$
	Me <sup>f</sup>	H			
	H Me <sup>g</sup>	Me Ph		0.26	0.05

<sup>a</sup> From (80AJC1763).<sup>b</sup>  $\sigma_p$ , 0.143 (84CB2275).<sup>c</sup>  $\sigma_p$ , 0.25 (74JCS(P2)449).<sup>d</sup> (81JCR(S)364).<sup>e</sup>  $\sigma_p$ , 0.28 (74JCS(P2)449).<sup>f</sup>  $\sigma_p$ , 0.33 (74JCS(P2)449).<sup>g</sup>  $\sigma_p$ , 0.235 (84CB2275).

To calculate the  $\sigma_I$  and  $\sigma_R^\circ$  constants for substituted *N*-azolyl groups, Fong used Eqs. (21) and (22) (80AJC1763).

The  $NH_2$  chemical shifts in the PMR spectra of *N*-(*p*-aminophenyl) derivatives of azoles were used to estimate the  $\sigma_p$  constants for some substituted *N*-azolyl groups (series 3; X = *N*-azolyl groups) (74JCS(P2)449). The  $\sigma_p$  constants for these groups are obtained also by alkaline hydrolysis of the corresponding phthalimide dyes (84CB2275).

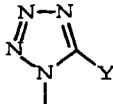
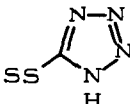
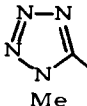
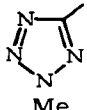
The  $\sigma$  constants for substituted 1-tetrazolyl groups have been estimated from  $^{19}F$  spectra of substituted fluorobenzenes (series 9; X = 1-tetrazolyl) (67JOC3580; 67MI2). To estimate the  $\sigma$  constants for the 2-chloro-1-tetrazolyl, and 1- and 2-methyl-5-tetrazolyl groups, use was also made of the ionization data of the respective tetrazolyanilines (series 3; X = tetrazolyl) and tetrazolylacetic acids (series 18) (67JOC3580; 67MI2; 83KGS1130).

The  $\sigma$  constants for substituted 1-tetrazolyl groups listed in Table XVIII indicate that by their inductive effect they are strong electron-withdrawing groups of similar strength to the  $NO_2$  group.

The reported values of  $\sigma_m$  and  $\sigma_p$  constants (67JOC3580; 67MI2) were used by Hansch to calculate the  $\mathcal{F}$  and  $\mathcal{R}$  constants for substituted 1-tetrazolyl groups (Table XVIII) (73JMC1207).



TABLE XVIII  
 $\sigma$  VALUES FOR SUBSTITUTED TETRAZOLYL GROUPS<sup>a</sup>

Group X		$\sigma_1$ ( $\sigma^*$ )	$\sigma_R^\circ$ ( $\sigma_R$ )	$\sigma_m$	$\sigma_p$	$\mathcal{F}^b$	$\mathcal{R}^b$	Method	Structural series (solvent)
	Y: Cl	0.69	(−0.02)	0.72	0.70	0.58	0.07	p <i>K</i> <sub>a</sub>	XC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub> (aq.)
		0.58	0.03	0.60	0.61			<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (MeCN)
		0.55	−0.01	0.54	0.54	0.53	0.05	<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (MeCN)
		0.45	0.00	0.45	0.45	0.44	0.05	<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (MeCN)
	N <sub>3</sub>	0.45	−0.12	0.39	0.33	0.40	−0.04	<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (acetone)
	SH								
	OH								
		0.62	0.02	0.63	0.64	0.61	0.07	<sup>19</sup> F	XC <sub>6</sub> H <sub>4</sub> F (MeCN)
		0.48 <sup>c</sup> (2.99) <sup>c</sup>						p <i>K</i> <sub>a</sub>	5-X-tetrazoles (aq.)
		0.32 <sup>c</sup> (1.99) <sup>c</sup>						p <i>K</i> <sub>a</sub>	5-X-tetrazoles (aq.)

<sup>a</sup> (67M12; 67JOC3580).

<sup>b</sup> (73JMC1207).

<sup>c</sup> (83KGS1130).

Using Charton's equation [Eq. (25)] for substituted acetic acids, Shchipanov calculated the  $\sigma_1$  constants for 1- and 2-methyl-5-tetrazolyl groups from the  $pK_a$  values of the corresponding tetrazolylacetic acids (83KGS1130). The  $\sigma^*$  constants for 1- and 2-methyl-5-tetrazolyl groups were determined by means of the equation  $\sigma_1 = \sigma^*/6.23$  (83KGS1130).

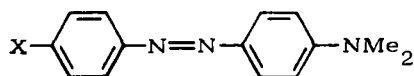
### 3. Fused Five-Membered Heteroaromatic Groups

There are data in the literature that make it possible to estimate the electronic effects of condensed systems containing a five-membered ring with one or more heteroatoms. These data are presented in Table XIX.

The  $\sigma_1$  constant for the 3-indolyl group has been estimated by Charton from the  $pK_a$  of indolyl-3-acetic acid in aqueous methyl Cellosolve® (64JOC1222).

The positive values of  $\sigma_1$  constants for heteroaromatic groups reported by Bystrov *et al.* (68ZOB1001) decrease in the sequence 2-benzoxazolyl > 2-benzothiazolyl > *N*-phenyl-2-benzimidazolyl > *N*-methyl-2-benzimidazolyl. The values of the  $\sigma_R^o$  constants decrease in the same sequence. This indicates the electron-releasing ability of condensed 2-hetaryls to increase in the above sequence, which conforms with their properties.

Yagupol'skii and Gandel'sman proposed to estimate the  $\sigma_p$  constants for substituents by using the interrelation between the difference in the absorption maxima of azo dyes (series 36) in neutral and acidic media, and  $\sigma_p$  con-



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stants [Eq. (31)] (65ZOB1252). In applying this dependence to 2-benzothiazolyl,

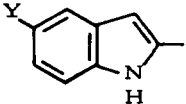
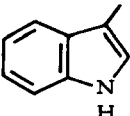
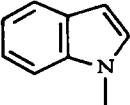
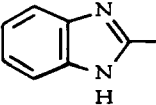
$$0.01 \Delta\lambda_{\max} = 1.25 - 1.01\sigma_p \quad (31)$$

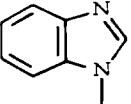
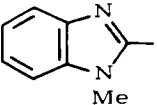
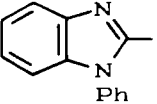
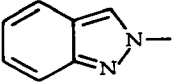
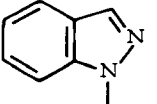
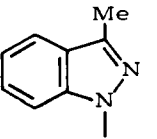
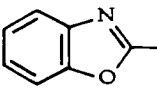
the  $\sigma_p$  constant obtained (0.36) (68ZOB1001) was close to the corresponding values determined from the  $pK_a$  of benzothiazolyl-2-acetic acid in aqueous ethanol and methyl Cellosolve® (0.29 and 0.34, respectively) (68ZOB1001).

Baram *et al.* (85IZV312) have determined the  $\sigma_1$  and  $\sigma_R^o$  constants for 5-substituted 2-indolyl groups on the basis of the  $^{13}\text{C}$ -NMR data on 5-substituted 2-phenylindoles (Table XIX).

To calculate the  $\sigma$  constants for 5-substituted 2-indolyl groups use was

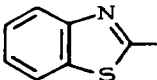
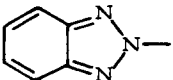
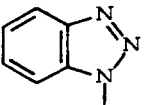
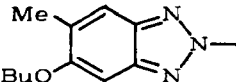
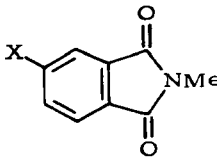
TABLE XIX  
 $\sigma$  VALUES FOR FUSED FIVE-MEMBERED HETEROAROMATIC GROUPS

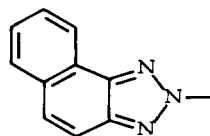
Group X		$\sigma_I$ ( $\sigma^*$ )	$\sigma_R^\circ$ ( $\sigma_R$ )	$\sigma_m$	$\sigma_p$	Method	Structural series (solvent)	Footnotes
	Y:H	0.19	-0.07			$^{13}\text{C}$	$\text{XC}_6\text{H}_5$ (acetone)	<i>a</i>
	Me	0.17	-0.08			$^{13}\text{C}$	$\text{XC}_6\text{H}_5$ (acetone)	<i>a</i>
	Cl	0.22	-0.06			$^{13}\text{C}$	$\text{XC}_6\text{H}_5$ (acetone)	<i>a</i>
	OMe	0.17	-0.07			$^{13}\text{C}$	$\text{XC}_6\text{H}_5$ (acetone)	<i>a</i>
	$\text{NH}_2$	0.15	-0.08			$^{13}\text{C}$	$\text{XC}_6\text{H}_5$ (acetone)	<i>a</i>
	$\text{NO}_2$	0.27	-0.04			$^{13}\text{C}$	$\text{XC}_6\text{H}_5$ (acetone)	<i>a</i>
	CN	0.25	-0.04			$^{13}\text{C}$	$\text{XC}_6\text{H}_5$ (acetone)	<i>a</i>
		-0.01				$\text{pK}_a$	$\text{XCH}_2\text{COOH}$ (aq. methyl Cellosolve*)	<i>b</i>
		0.01				$\text{pK}_a$	$\text{XCH}_2\text{COOH}$ (aq.)	<i>c</i>
		0.33				$\text{pK}_a$	$\text{XCH}_2\text{COOH}$ (aq. EtOH)	<i>d</i>
		(2.05)						
		0.28				$\text{pK}_a$	$\text{XCH}_2\text{COOH}$ (aq. EtOH)	<i>e</i>
		(1.75)						
			-0.49			$^{13}\text{C}$	$\text{XCH}=\text{CH}_2$	<i>d</i>
			-0.44			$A_{1640}$	$\text{XCH}=\text{CH}_2$ ( $\text{CCl}_4$ )	<i>f</i>
			0.05			$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$	<i>g</i>
				-0.726		$\text{pK}_a$	$\text{XC}_6\text{H}_4\text{NH}_2$ (DMF)	<i>h</i>

					0.38 0.50	$^1\text{H}$ $\nu_{\text{as-NH}_2}$	$\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO) $\text{XC}_6\text{H}_4\text{NH}_2$ ( $\text{CCl}_4$ )	<i>i</i> <i>i</i>
		0.07	-0.40 0.04			$A_{1640}$ $^{19}\text{F}$	$\text{XCH}=\text{CH}_2$ ( $\text{CCl}_4$ ) $\text{XC}_6\text{H}_4\text{F}$ (heptane)	<i>f</i> <i>j</i>
	<i>k</i>	0.14 0.18 0.15	0.08 0.05 0.10	0.17  0.19	-0.364 0.21 0.24	$\text{pK}_a$ $\text{pK}_a$ $^{19}\text{F}$ $\text{pK}_a$	$\text{XC}_6\text{H}_4\text{NH}_2$ (DMF) $\text{XC}_6\text{H}_4\text{COOH}$ (aq. EtOH) $\text{XC}_6\text{H}_4\text{F}$ (heptane) $\text{XC}_6\text{H}_4\text{COOH}$ (aq. methyl Cellosolve <sup>®</sup> )	<i>h</i> <i>j</i> <i>j</i> <i>j</i>
		0.420	-0.126			$^{19}\text{F}$	$\text{XC}_6\text{H}_4\text{F}$ ( $\text{CDCl}_3$ or $\text{CD}_3\text{CN}$ )	<i>l</i>
		0.361	-0.154 -0.49			$^{19}\text{F}$ $A_{1640}$	$\text{XC}_6\text{H}_4\text{F}$ ( $\text{CDCl}_3$ or $\text{CD}_3\text{CN}$ ) $\text{XCH}=\text{CH}_2$ ( $\text{CCl}_4$ )	<i>l</i> <i>f</i>
					0.27 0.25	$^1\text{H}$ $\nu_{\text{as-NH}_2}$	$\text{XC}_6\text{H}_4\text{NH}_2$ (DMSO) $\text{XC}_6\text{H}_4\text{NH}_2$ ( $\text{CCl}_4$ )	<i>i</i> <i>i</i>
	<i>m</i>	0.26 0.28	0.14 0.14 0.06	0.31	0.34	$^{19}\text{F}$ $^{19}\text{F}$ $\text{pK}_a$	$\text{XC}_6\text{H}_4\text{F}$ $\text{XC}_6\text{H}_4\text{F}$ (heptane) $\text{XC}_6\text{H}_4\text{COOH}$ (aq. methyl Cellosolve <sup>®</sup> )	<i>n</i> <i>j</i> <i>j</i>

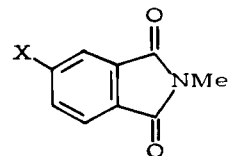
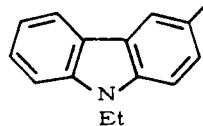
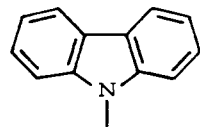
(continued)

TABLE XIX (continued)

Group X	$\sigma_I$ ( $\sigma^*$ )	$\sigma_R^\circ$ ( $\sigma_R$ )	$\sigma_m$	$\sigma_p$	Method	Structural series (solvent)	Footnotes	
	<i>o</i>	0.28	0.05	0.30	0.33	$pK_a$	$XC_6H_4COOH$ (aq. EtOH)	<i>j</i>
			0.10			$^{19}F$	$XC_6H_4F$	<i>n</i>
		0.24	0.10			$^{19}F$	$XC_6H_4F$ (heptane)	<i>j</i>
		0.31	0.03	0.33	0.34	$pK_a$	$XC_6H_4COOH$ (aq. methyl Cellosolve <sup>®</sup> )	<i>j</i>
		0.26	0.03	0.27	0.29	$pK_a$	$XC_6H_4COOH$ (aq. EtOH)	<i>j</i>
				0.26	$pK_a$	$X-(C_4H_2O)CH=CHCOOH$ (aq. methyl Cellosolve <sup>®</sup> )	<i>p</i>	
				0.36	$\lambda_{max}$	$XC_6H_4N=NC_6H_4NMe_2$	<i>j</i>	
			0.517	0.566	$pK_a$	$XC_6H_4OH$	<i>q</i>	
			0.491	0.508	$pK_a$	$XC_6H_4NH_2$	<i>q</i>	
			0.537	0.450	$\nu_{s-NH_2}$	$XC_6H_4NH_2$ (CCl <sub>4</sub> )	<i>q</i>	
			0.519	0.461	$\nu_{as-NH_2}$	$XC_6H_4NH_2$ (CCl <sub>4</sub> )	<i>q</i>	
	0.550	-0.32			$A_{1640}$	$XCH=CH_2$ (CCl <sub>4</sub> )	<i>f</i>	
		-0.097			$^{19}F$	$XC_6H_4F$ (CDCl <sub>3</sub> or CD <sub>3</sub> CN)	<i>l</i>	
				0.306	log <i>k</i>	 (methyl Cellosolve <sup>®</sup> )	<i>r</i>	



0.309

log *k*(methyl Cellosolve<sup>®</sup>)*r*0.02  
(0.15)*pK<sub>a</sub>**XCH<sub>2</sub>COOH* (aq. EtOH)*e*0.25  
(1.55)*pK<sub>a</sub>**XCH<sub>2</sub>COOH* (aq. EtOH)*e*

0.48

0.385

<sup>1</sup>H(*J<sub>H-H</sub>*)*XCH=CH<sub>2</sub>**s*

0.43

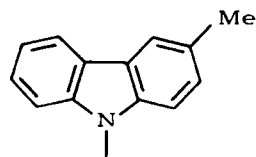
<sup>1</sup>H*XC<sub>6</sub>H<sub>4</sub>NH<sub>2</sub>* (DMSO)*i**ν<sub>as-NH<sub>2</sub></sub>**XC<sub>6</sub>H<sub>4</sub>NH<sub>2</sub>* (CCl<sub>4</sub>)*i**pK<sub>a</sub>**XCH<sub>2</sub>COOH* (aq. EtOH)*d*0.31  
(1.92)<sup>13</sup>C*XCH=CH<sub>2</sub>* (CCl<sub>4</sub>)*d*

0.412

-0.41

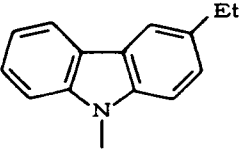
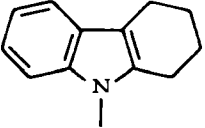
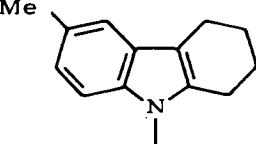
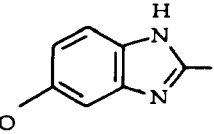
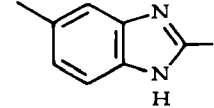
<sup>19</sup>F*XC<sub>6</sub>H<sub>4</sub>F* (CDCl<sub>3</sub> or CD<sub>3</sub>CN)*l*

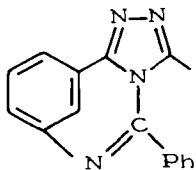
-0.115

0.23  
(1.45)*pK<sub>a</sub>**XCH<sub>2</sub>COOH* (aq. EtOH)*d*

(continued)

TABLE XIX (continued)

Group X	$\sigma_I$ ( $\sigma^*$ )	$\sigma_R^\circ$ ( $\sigma_R$ )	$\sigma_m$	$\sigma_p$	Method	Structural series (solvent)	Footnotes
	0.23 (1.43)				$pK_a$	$XCH_2COOH$ (aq. EtOH)	<i>e</i>
	0.28 (1.74)				$pK_a$	$XCH_2COOH$ (aq. EtOH)	<i>d</i>
	0.22 (1.36)				$pK_a$	$XCH_2COOH$ (aq. EtOH)	<i>d</i>
				0.439	log <i>k</i>	$XC_6H_4NH_2$	<i>t</i>
				0.453	log <i>k</i>	$XC_6H_4NH_2$	<i>t</i>



0.277

$pK_a$

$XC_6H_4NH_2$  (DMF)

*h*

<sup>a</sup> (85IZV312).

<sup>b</sup> (64JOC1222).

<sup>c</sup> (81MI1).

<sup>d</sup> (83KGS369).

<sup>e</sup> (81KGS1654).

<sup>f</sup> (80IZV1562).

<sup>g</sup> (79KGS1155).

<sup>h</sup> (81ZOB192).

<sup>i</sup> (74JCS(P2)449).

<sup>j</sup> (68ZOB1001).

<sup>k</sup>  $\mathcal{F} = 0.15$ ,  $\mathcal{R} = 0.08$  (73JMC1207).

<sup>l</sup> (81JCR(S)364).

<sup>m</sup>  $\mathcal{F} = 0.28$ ,  $\mathcal{R} = 0.07$  (73JMC1207).

<sup>n</sup> (76KGS906).

<sup>o</sup>  $\mathcal{F} = 0.25$ ,  $\mathcal{R} = 0.06$  (73JMC1207).

<sup>p</sup> (77CCC1871).

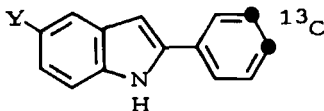
<sup>q</sup> (69CCC72).

<sup>r</sup> (84CB2275).

<sup>s</sup> (81T929).

<sup>t</sup> (74ZOR1896).





( 37 )

$\text{Y} = \text{H, Me, Cl, OMe, NH}_2, \text{CN, NO}_2$

made of the correlation equations for monosubstituted benzenes (37) (82MI1).

From the data presented in Table XIX for 5-substituted 2-indolyl groups, it can be concluded that by their inductive effect they are electron-withdrawing substituents, and that by their mesomeric effect they are weak electron-releasing substituents comparable to *m*- and *p*-substituted phenyl groups with electron-releasing substituents.

#### IV. Estimation of the Electronic Effects of Substituted Phenyl and Heteroaromatic Groups

##### A. SEPARATION OF $\sigma$ CONSTANTS FOR SUBSTITUTED GROUPS INTO CONTRIBUTIONS FROM UNSUBSTITUTED GROUPS AND SUBSTITUENTS

In practice an investigator has to deal with derivatives of substituted heterocycles in which a substituted heteroaromatic group can be regarded as a substituent. For a variety of such composite groups, the  $\sigma$  constants are undetermined due to experimental difficulties. In these instances the constants for composite substituents must be estimated from the constants for their constituents.

Successful attempts to evaluate  $\sigma$  constants for composite substituents were made by Charton (63JOC3121). For calculating the Hammett constants  $\sigma(\text{YG})$  for YG-type substituents where G is a skeletal group ( $\text{C}=\text{O}$ , O, NH, S) he suggested Eq. (32).

$$\sigma(\text{YG}) = m\sigma(\text{Y}) + c \quad (32)$$

This principle was further developed by Mamaev and co-workers (79MI2; 80IZV1781; 82DOK99; 85IZV312; 85MI3) and Charton (81MI1). They suggested an approach based on separating the  $\sigma_1$  and  $\sigma_R$  constants for composite substituents into inductive and resonance constituents. This is illustrated by examples for the substituted phenyl and heteroaromatic groups.

##### 1. Substituted Phenyl Groups

Mamaev and co-workers proceeded from the fact that the mesomeric effect of a substituted phenyl group must reflect the perturbation of the  $\pi$ -electron

system in the benzene ring under the action of the substituent, the perturbation being affected by the interaction through both the inductive mechanism and that of conjugation. For an estimation of the inductive effect of a substituted phenyl group it is essential that the charges should be distributed over the  $\sigma$ -framework and the  $\pi$ -system of the benzene ring (82DOK99;83IZV294). As the distribution of these charges is influenced by both electronic effects of the substituent, the inductive effect of the substituted phenyl group must also be dependent on the inductive and the mesomeric effect of the substituent. From these general considerations, the  $\sigma_I$  and  $\sigma_R^\circ$  constants for substituted phenyl groups (PhY) were separated into the corresponding constant ( $\sigma_I$  or  $\sigma_R^\circ$ ) for the unsubstituted phenyl group (Ph) and into contributions proportional to the  $\sigma_I$  and  $\sigma_R^\circ$  constants for substituent Y [Eqs. (33) and (34)]. The coefficients in these equations were determined using the method of dual-variable parameter corelation.

$$\sigma_I(\text{PhY}) = \sigma_I(\text{Ph}) + a'_{\text{Ph}}\sigma_I(\text{Y}) + b'_{\text{Ph}}\sigma_R^\circ(\text{Y}) \quad (33)$$

$$\sigma_R^\circ(\text{PhY}) = \sigma_R^\circ(\text{Ph}) + a''_{\text{Ph}}\sigma_I(\text{Y}) + b''_{\text{Ph}}\sigma_R^\circ(\text{Y}) \quad (34)$$

For <i>m</i> -YC <sub>6</sub> H <sub>4</sub> —	$a_{\text{Ph}}$	$b_{\text{Ph}}$	$r$	$s$	$n$
Eq. (33)	0.16	0.14	0.995	0.008	8
Eq. (34)	0.05	0.01	0.990	0.002	8
For <i>p</i> -YC <sub>6</sub> H <sub>4</sub> —					
Eq. (33)	0.12	0.20	0.993	0.009	9
Eq. (34)	0.05	0.10	0.994	0.004	9

As seen from the listed coefficients, comparable contributions to the  $\sigma_I$  constant (PhY) characterizing the inductive effect of the substituted phenyl group are made by both the inductive and the mesomeric effect of the Y substituent. In the case of the *p*-substituted phenyl group, the influence of the inductive effect of the Y substituent is lower and that of the mesomeric effect is higher than for the *m*-substituted phenyl group. The  $\sigma_R^\circ(\text{PhY})$  constant characterizing the mesomeric effect for the *m*-substituted phenyl group proved to depend little on either effect of the Y substituent, whereas for the *p*-substituted phenyl group, the largest contribution is made by the mesomeric effect of the Y substituent. The  $\sigma_I$  and  $\sigma_R$  constants for *m*- and *p*-substituted phenyl groups have been shown by Charton to correlate well with the  $\sigma_I$  and  $\sigma_R^\circ$  constants for the substituent (81M11). The author suggests that Eqs. (35)–(37) should be used to evaluate the  $\sigma_I$  and  $\sigma_R$  constants for other substituted phenyl groups.

$$\sigma_I(\text{PhY}) = a'_{\text{Ph}}\sigma_I(\text{Y}) + b'_{\text{Ph}}\sigma_R^\circ(\text{Y}) + c' \quad (35)$$

$$\sigma_R(\text{PhY}) = a''_{\text{Ph}}\sigma_I(\text{Y}) + b''_{\text{Ph}}\sigma_R^\circ(\text{Y}) + c'' \quad (36)$$

$$\sigma_R^+(\text{PhY}) = a'''_{\text{Ph}}\sigma_I(\text{Y}) + b'''_{\text{Ph}}\sigma_R^+(\text{Y}) + c''' \quad (37)$$

For <i>m</i> -YC <sub>6</sub> H <sub>4</sub> —	<i>a</i> <sub>Ph</sub>	<i>b</i> <sub>Ph</sub>	<i>c</i>	<i>r</i>	<i>s</i>	<i>n</i>
Eq. (35)	0.112	0.0474	0.120	0.9989	0.0019	5
Eq. (36)	0.153	0.0761	−0.110	0.9993	0.00281	4
For <i>p</i> -YC <sub>6</sub> H <sub>4</sub> —						
Eq. (35)	0.138	0.137	0.120	0.9954	0.00431	11
Eq. (36)	0.180	0.111	−0.0988	0.9661	0.0155	9
Eq. (37)	0.139	0.218	−0.167	0.9983	0.00427	5

The free terms in the Charton equations are in fact the values of the corresponding constants for the unsubstituted phenyl group, just as in Eqs. (33) and (34). The fact that the *a* and *b* coefficients in Eqs. (35) and (36) are different

TABLE XX  
PARAMETERS OF EQS. (38) AND (39) FOR SUBSTITUTED PYRIMIDINYL GROUPS BASED ON  
<sup>13</sup>C-NMR DATA

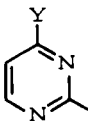
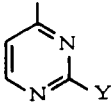
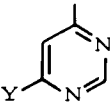
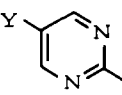
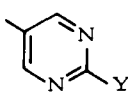
Group	Equation	Solvent	<i>a</i>	<i>b</i>	<i>r</i>	<i>s</i>
	38	Acetone	0.22	0.25	0.990	0.021
	38	DMSO	0.19	0.23	0.989	0.019
	39	Acetone	0.08	0.02	0.996	0.002
	39	DMSO	0.08	0.02	0.996	0.002
	38	Acetone	0.22	0.23	0.988	0.022
	38	DMSO	0.22	0.19	0.990	0.017
	39	Acetone	0.08	0.03	0.990	0.004
	39	DMSO	0.08	0.02	0.990	0.004
	38	Acetone	0.19	0.29	0.984	0.027
	38	DMSO	0.16	0.27	0.999	0.005
	39	Acetone	0.07	0.04	0.996	0.003
	39	DMSO	0.07	0.06	0.991	0.005
	38	Acetone	0.14	0.22	0.998	0.007
	39	Acetone	0.06	0.11	0.991	0.007
	38	Acetone	0.12	0.21	0.996	0.009
	39	Acetone	0.05	0.11	0.992	0.006

from coefficients in Eqs. (33) and (34) may be due to a very limited number of correlated magnitudes and their insufficient diversity.

## 2. Substituted Pyrimidinyl Groups

The approach based on separating the  $\sigma$  constants for composite substituents into their constituents was used to obtain correlation Eqs. (38) and (39) for evaluating the  $\sigma$  constants for substituted pyrimidinyl groups (PymY) (79MI2; 80IZV1781; 82DOK99; 83IZV299; 83MI1; 85MI3). The values of the constants for the substituted pyrimidinyl groups found by  $^{13}\text{C}$  and  $^{19}\text{F}$  NMR (Table XII) were used to calculate the  $a$  and  $b$  coefficients in Eqs. (38) and (39). The parameters of these correlation equations are listed in Tables XX and XXI. Analysis of these parameters shows the inductive and mesomeric effects of the Y substituent to make essentially comparable contributions to the  $\sigma_i(\text{PymY})$  constant characterizing the inductive effect of substituted pyrimidinyl groups. The  $\sigma_R^\circ(\text{PymY})$  constant characterizing the mesomeric

TABLE XXI  
PARAMETERS OF EQS. (38) AND (39) FOR SUBSTITUTED PYRIMIDINYL GROUPS BASED ON  
 $^{19}\text{F}$ -NMR DATA

Group	Equation	Solvent	$a$	$b$	$r$	$s$
	38	$\text{CCl}_4$	0.23	0.25	0.999	0.005
	38	DMSO	0.13	0.18	0.988	0.007
	39	$\text{CCl}_4$	0.12	0.05	0.999	0.007
	39	DMSO	0.11	0.03	0.989	0.012
	38	$\text{CCl}_4$	0.25	0.09	0.998	0.005
	38	DMSO	0.18	0.07	0.988	0.009
	39	$\text{CCl}_4$	0.09	0.06	0.988	0.009
	39	DMSO	0.10	0.04	0.985	0.008
	38	$\text{CCl}_4$	0.25	0.21	0.999	0.004
	38	DMSO	0.17	0.16	0.995	0.007
	39	$\text{CCl}_4$	0.10	0.12	0.995	0.007
	39	DMSO	0.11	0.09	0.998	0.002
	38	$\text{CCl}_4$	0.18	0.19	0.990	0.012
	38	DMSO	0.14	0.13	0.995	0.004
	39	$\text{CCl}_4$	0.07	0.15	0.995	0.007
	39	DMSO	0.10	0.18	0.990	0.009
	38	$\text{CCl}_4$	0.23	0.30	0.989	0.020
	38	DMSO	0.04	0.12	0.991	0.006
	39	$\text{CCl}_4$	0.06	0.13	0.989	0.009
	39	DMSO	0.06	0.14	0.988	0.010

effect of the same groups depends relatively little on either the inductive or the mesomeric effect of the Y substituent.

$$\sigma_1(\text{PymY}) = \sigma_1(\text{Pym}) + a'\sigma_1(\text{Y}) + b'\sigma_{\text{R}}^{\circ}(\text{Y}) \quad (38)$$

$$\sigma_{\text{R}}^{\circ}(\text{PymY}) = \sigma_{\text{R}}^{\circ}(\text{Pym}) + a''\sigma_1(\text{Y}) + b''\sigma_{\text{R}}^{\circ}(\text{Y}) \quad (39)$$

### 3. Substituted Quinazolinyl and Indolyl Groups

The approach developed for estimating the  $\sigma_1$  and  $\sigma_{\text{R}}^{\circ}$  constants for substituted phenyl and pyrimidinyl groups was extended by Mamaev and co-workers to other substituted heteroaromatic groups, in particular substituted quinazolinyl (QuinY) (85MI3; 85MI14) and indolyl (IndY) groups (85IZV312; 85MI3). Analogously to those described in Sections IV,A,1 and IV,A,2, the coefficients in Eqs. (40) and (41), and (42) and (43), were determined.

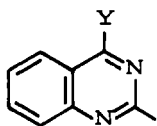
$$\sigma_1(\text{QuinY}) = \sigma_1(\text{Quin}) + a'\sigma_1(\text{Y}) + b'\sigma_{\text{R}}^{\circ}(\text{Y}) \quad (40)$$

$$\sigma_{\text{R}}^{\circ}(\text{QuinY}) = \sigma_{\text{R}}^{\circ}(\text{Quin}) + a''\sigma_1(\text{Y}) + b''\sigma_{\text{R}}^{\circ}(\text{Y}) \quad (41)$$

$$\sigma_1(\text{IndY}) = \sigma_1(\text{Ind}) + a'\sigma_1(\text{Y}) + b'\sigma_{\text{R}}^{\circ}(\text{Y}) \quad (42)$$

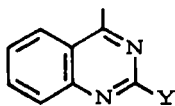
$$\sigma_{\text{R}}^{\circ}(\text{IndY}) = \sigma_{\text{R}}^{\circ}(\text{Ind}) + a''\sigma_1(\text{Y}) + b''\sigma_{\text{R}}^{\circ}(\text{Y}) \quad (43)$$

For



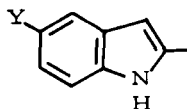
	<i>a</i>	<i>b</i>	<i>r</i>	<i>s</i>	<i>n</i>
Eq. (40)	0.21	0.24	0.990	0.021	5
Eq. (41)	0.07	0.02	0.992	0.003	5

For



	<i>a</i>	<i>b</i>	<i>r</i>	<i>s</i>	<i>n</i>
Eq. (40)	0.21	0.21	0.989	0.022	5
Eq. (41)	0.08	0.03	0.991	0.004	5

For

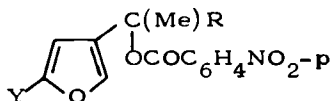


	<i>a</i>	<i>b</i>	<i>r</i>	<i>s</i>	<i>n</i>
Eq. (42)	0.10	0.09	0.993	0.006	7
Eq. (43)	0.05	0.03	0.992	0.003	7

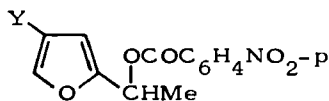
The data presented in this section indicate that the approach suggested for estimating the constants for composite substituents is general and that it can be used to estimate the  $\sigma$  constants for other composite substituents, provided the  $\sigma$  constants for the corresponding unsubstituted heteroaromatic groups are known and the values of the  $\sigma_1$  and  $\sigma_R^\circ$  constants for the Y substituent in the heterocycle are available.

## B. PECULIARITIES OF THE ELECTRONIC EFFECTS OF SUBSTITUENTS IN HETEROAROMATIC RINGS

The electronic effects of substituents in heteroaromatic rings is closely connected with the specificity of the electron distribution in the latter as transmitters of electronic effects. The reviews (64AHC(3)209; 76AHC(20)1; 86RCR769) describe in detail numerous examples of applying the Hammett equation to the reactivity parameters and the physical characteristics of the derivatives of five-membered heterocycles by using tabulated  $\sigma$  values determined for the benzene series. As a rule,  $\sigma_p$  constants can be successfully used for 2,5-disubstituted, and  $\sigma_m$  constants for 2,4-disubstituted compounds. The high correlation coefficients point to the balance maintained between the inductive and resonance contributions to substituent effects both in five-membered heteroaromatic and in benzene rings. Nevertheless, Noyce and Pavez, studying the solvolysis of  $\alpha$ -chloro- and  $\alpha$ -(*p*-nitrobenzoyloxy)alkyl derivatives of heterocycles, revealed certain anomalies in the reactivity of some heterocyclic series. Thus, in the furan series (38), the solvolysis rate constants correlate neither with  $\sigma_m$  nor with  $\sigma_m^+$  constants for substituents (72JOC2620). In this series the resonance constituent fraction in the total substituent effect was shown by them to be appreciably greater than that in the isomeric furan series (39) and in the similar *m*-benzene and thiophene series (72JOC2623).

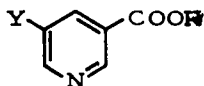


R = H, Me ( 38 )

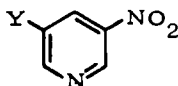


( 39 )

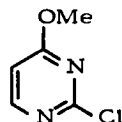
In the series of six-membered heteroaromatic systems, those best studied are the azines. We have previously discussed in detail the instances of specific substituent effects in the pyridine, quinoline, pyridazine, phtalazine, pyrimidine, and *s*-triazine rings available in the literature in a brief review devoted to the transmission of substituent effects in the azinyl series (80MI1). The data indicate that, in the absence of cross-conjugation among substituent, reaction site, and ring heteroatom, the benzenoid  $\sigma$  values describe satisfactorily the variation in the reactivity of substituted azines. As an example, one can cite the data on the rates of the esterification of 5-substituted nicotinic acids (**40**) with diazodiphenylmethane (78JCS(P2)34; 84JCS(P2)1975), the alkaline hydrolysis of their methyl (**41**) and ethyl (**42**) esters (67NKZ1210; 70JCS(B)1063), as well as the data on the ionization of the same acids (**40**) (67NKZ1210) and the polarographic reduction of 5-substituted 3-nitropyridines (**43**) (73AC(R)121).



R = H ( 40 )



( 43 )



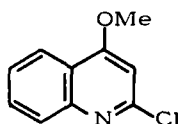
( 44 )

R = Me ( 41 )

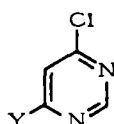
R = Et ( 42 )

If the substituent is ortho or para to the nitrogen heteroatom, the rate of nucleophilic substitution is decreased rather markedly by substituents with a +M effect, despite the absence of direct conjugation between these and the reaction site. Illuminati connected the nature of this effect, referred to as the *effect of indirect deactivation*, with the manifestation of direct conjugation of +M substituents with an electron-withdrawing nitrogen heteroatom. All this leads to a decreased activating ability of the latter (64AHC(3)285). In estimating the relative rates of methoxy-dechlorination in the series of 2- and 4-chloroquinolines, the *m*-MeO group from the 4- and 2-position, respectively, was found to deactivate the chlorine atom markedly more than one could expect judging by its  $\sigma_m$  constant. The effect of indirect deactivation

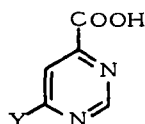
proved to be also peculiar to other substituents possessing a mesomeric electron-releasing character, in which case  $\text{MeO}$ ,  $\text{EtO} > \text{SMe}$ ,  $\text{Cl} > \text{Me}$ . Illuminati and co-workers estimated quantitatively the decrease, under the effect of an *m*- $\text{MeO}$  group, in the relative rate of methoxy-dechlorination of 2-chloro-4-methoxypyridine (44) and -quinoline (45) in terms of the *deactivation factor* (1.4 and 4.6, respectively) and pointed to an analogy with the behavior of nitro-activated aromatic chloro derivatives.



( 45 )



Y = Me ( 46 )



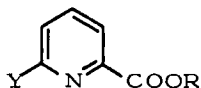
( 48 )

Y = OMe ( 47 )

This effect is particularly pronounced in 4-chloro-6-methoxypyrimidine (47), in which the deactivating factor is about 37 (69JHC879). The deactivating ability of the 6-OMe group was found to be higher than that of the 2-OMe group in the side-chain diazo-coupling reaction of substituted 4-methylpyrimidines (70KGS1573). The deactivating effect of the 6-Me group on the reactivity of 4-chloropyrimidine (46) also turned out to be higher than that of the 2-Me group: the decrease in the relative rates is 1.57-fold for piperidino-dechlorination in toluene and 1.40-fold in EtOH (67T813). This conclusion is corroborated when comparing the substituent effect on the ionization constants of 6-substituted 2-pyrimidinecarboxylic acids (48) and meta-substituted benzoic acids (72KGS558).

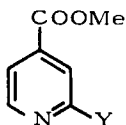
For methyl picolines (50) and isonicotines (51) with substituents at  $\alpha$ -positions in the ring, the correlations of alkaline hydrolysis rate constants with the  $\sigma_m$  values proved quite unsatisfactory, the greatest deviations being recorded for derivatives having substituents with a high +M effect. Thus, 6-methoxy picolinate (50, Y = OMe) and 2-methoxy isonicotinate (51, Y = OMe) are hydrolyzed at rates that are about one-half those expected from additive effects of methoxy and aza substituents (70JCS(B)1065). Interestingly, the difference between  $\log k$  for 4- and 6-substituted picolines with the same substituents is proportional to the  $\sigma_R^0$  values, which are the characteristics of the mesomeric properties of substituents. Similar rate anomalies have been observed in the reactions of some 4-substituted (52) and 6-substituted (49) picolinic acids with diazophenylmethane (78JCS(P2)34), as well as in  $E_{1/2}$  magnitudes for polarographic reduction of some 4-substituted 2-nitropyridines (77MI1) and 2-phenylazopyridines (79MI3).



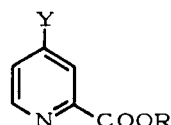


R = H (49)

R = Me (50)



(51)



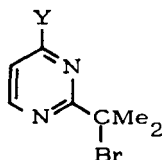
R = H (52)

R = Me (53)

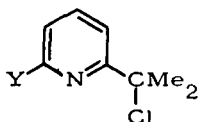
The generality of the phenomenon of indirect deactivation was demonstrated by Minisci *et al.* in the reaction of homolytic alkylation of protonated pyridines and quinolines (71CI(M)263; 71T3655; 72T2403). The attacking alkyl radical was found to behave like a nucleophilic reagent and to attack selectively the most electron-deficient position 2 in the cation of 4-substituted pyridine or quinoline. However, the reaction rates correlate poorly with  $\sigma_m$  substituent constants, the deviations of points from the correlation straight line increasing in the sequence  $\text{Me} < \text{Cl} < \text{MeO}$ . Thus, the substrate is strongly deactivated by MeO groups and insufficiently activated by a chlorine atom.

The effect of indirect deactivation can manifest itself in all reactions passing through the stage of forming a negatively charged intermediate or through a transition state in which a negative charge develops at the reaction center. The reaction center may be located in the heteroaromatic ring (for aromatic nucleophilic and radical substitution), near the ring (reduction of nitro derivatives, acid ionization of amino derivatives), or in an aliphatic and an aromatic side chain (H-exchange of alkyl derivatives, ionization of acids, hydrolysis of their esters, etc.). The correlation straight lines characterizing the dependence of kinetic and thermodynamic parameters of these reactions on the substituent electronic effects have a positive slope, which corresponds to the destabilizing effect of electron-releasing substituents and to the stabilizing effect of electron-withdrawing ones.

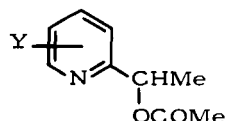
By contrast, in other reactions that pass through a transition state or an intermediate with a positive charge at the reaction center, the presence of substituents with a +M effect in the heteroaromatic ring leads to an increase in the reaction rate as compared with similar derivatives of the benzene series (effect of indirect activation). This accelerating effect of the m-MeO group was discovered when studying the kinetics of solvolysis of 4-substituted 2-( $\alpha$ -bromoisopropyl)pyrimidines (**54**) (77AJC1785; 78AJC1391) and 6-substituted 2-( $\alpha$ -chloroisopropyl)pyridines (**55**) (72TL3893; 73JOC2660), and the kinetics of pyrolytic deacetoxylation of 4- and 6-substituted 2-( $\alpha$ -acetoxyethyl)pyridines (**56**) in the gas phase (79JCS(P2)624).



( 54 )



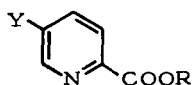
( 55 )



( 56 )

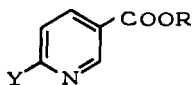
It is evident that the manifestations of indirect deactivation and indirect activation are due to the substituent resonance effect and virtually point to increased transfer of the resonance effect to the reaction site.

The situation is simplified if the substituent is at a para position to the reaction site since in this case there are no conditions for realizing the indirect resonance effect. The substituent and the reaction site cannot be simultaneously directly conjugated with the nitrogen heteroatom of the azine ring and, as a rule, the reactivity parameters correlate well with the Hammett  $\sigma_p$  values. Examples include (1) the ionization constants of 5-substituted picolinic (**57**) and 6-substituted nicotinic acids (**59**) (59NKZ1293); (2) the rates of alkaline hydrolysis of 5-substituted methyl picolinates (**58**) (70JCS(B)1063); (3) the half-wave potentials for polarographic reduction of 5-substituted 2-nitropyridines (**61**) and 6-substituted 3-nitropyridines (**62**) (73AC(R)135); (4) the kinetic data for radical alkylation of 3-substituted pyridines proceeding selectively at the 6-position of the pyridine ring (74T4201); and (5) the rates of solvolysis of 5-substituted 2-( $\alpha$ -chloroethyl)pyridines (72TL3893). For 6-substituted methyl nicotines (**60**), the correlation proves to be poor, with the greatest deviations of values for +M substituents (70JCS(B)1065).



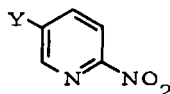
R = H ( 57 )

R = Me ( 58 )

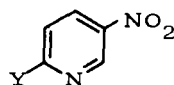


R = H ( 59 )

R = Me ( 60 )



( 61 )

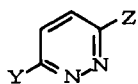


( 62 )

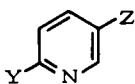
In an analysis of analogous data for pyridazine derivatives, i.e., 3,6-disubstituted pyridazines (**63**), where Z is a reaction site, both situations with respect to each nitrogen heteroatom (structures **64** and **65**) can be considered separately and their effects can be regarded as additive.

This approach is confirmed by good correlations of the methoxy-dechlorination rates for 6-substituted 3-chloropyridazines (series **63**, Z = Cl)

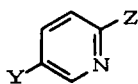
(64JOC1642) and 4-substituted 1-chlorophthalazines (66) (71JOC3248) with  $\sigma_p$  substituent constants.



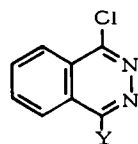
( 63 )



( 64 )

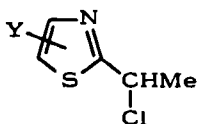


( 65 )



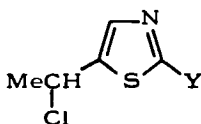
( 66 )

In studying the peculiarities of the electronic influence of substituents in azoles, note should be made of the similarity between the latter and azines. Thus, the rates of solvolysis of the two thiazoles series **68** and **69** in 80% aq. EtOH are well correlated with the Brown–Okamoto substituent constants,  $\sigma_p^+$  (73JOC3318), whereas the correlations of the reaction rates for series **70** with the  $\sigma_m$  or  $\sigma_m^+$  constants are clearly unsatisfactory (73JOC3321). However, highly satisfactory results are obtained involving very good correlation for this series with reactivities observed for similar pyridine series (**55**). The common feature of these two families, with the substituent and reacting side chain flanking the nitrogen heteroatom, is due to the dominating resonance component of the total substituent effect (73JOC3321).

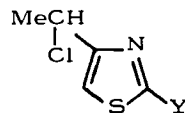


4-Y ( 67 )

5-Y ( 68 )



( 69 )

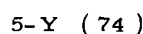
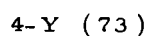
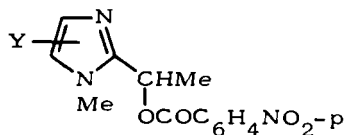
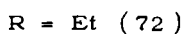
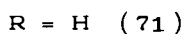
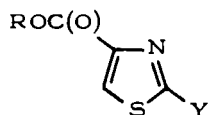


( 70 )

The kinetic evidence available for three representatives of the isomeric thiazole series (**67**) allows this conclusion to be extended to this series as well (73JOC3321). One can agree with the view expressed in the above paper that the former conclusion of Imoto and Otsuji as to the applicability of the Hammett equation to the data on saponification of 2-substituted ethyl 4-thiazolecarboxylates (**72**) and to  $pK_a$  values of the corresponding acids (**71**) (58MI1) is questionable because the amino group has been the only strong electron-releasing substituent investigated by them (73JOC3321).

In the imidazole system the effect of 5-substituents on the rates of solvolysis of 2-nitrobenzoyloxyethyl derivatives (**74**) correlates fairly well with  $\sigma_p^+$  constants, but for the 4-substituents (**73**) the correlation with  $\sigma_m^+$  constants is poor and the reaction rates are higher than the ones that can be

calculated according to their  $\sigma_m^+$  constants (73JOC3762). A comparative analysis of the kinetic data allows one to conclude that the resonance stabilization by the 4-substituents of the reaction site in 2,4-disubstituted imidazoles is higher than that in similar thiazoles and in 2,6-disubstituted pyridines (73JOC3762).



The above data on the specificity of substituent effects in heteroaromatic rings points to the desirability (and in many instances also to the necessity) of dividing electronic effects into inductive and resonance constituents, since their balance not only differs from that in the benzene ring, but also varies for one and the same heterocycle, depending on the relative positions of substituent, heteroatom, and reaction site. There are two points of view on the question of applying the Hammett equation to heterocyclic compounds. According to one, the description of substituent effect requires special sets of different  $\sigma$  constants, which involves many methodological and experimental difficulties. The alternative viewpoint assumes it is possible to use the  $\sigma$  constants of the benzene series, and takes into account the changes in their electronic effects by introducing correction coefficients for the inductive and resonance constituents. Such correction coefficients (or *transmission factors*  $\gamma_I$  and  $\gamma_R$ ) characterize the sensitivity of the aromatic system to the transfer of electronic substituent effects by means of inductive and conjugative mechanisms and are presented as fractions of the transmission of the same effects through the benzene ring which is chosen as the standard. In this approach, under the identical conditions (reagent, character and type of reaction center in the molecule, solvent, temperature, etc.), one and the same method is used to determine the coefficients of dual-parameter correlation equations for the benzene and the heteroaromatic series, and then to calculate, from the ratios of these coefficients, the transmission factors [Eqs. (44) and (45)].

$$\gamma_I^{ij} = \rho_I^{ij}/\rho_I \quad (44)$$

$$\gamma_R^{ij} = \rho_R^{ij}/\rho_R \quad (45)$$

The index  $i$  marks the position of the substituent and  $j$  that of the probe or reaction site in the heterocycle. Strictly speaking, in all cases we recommend to use as a standard the same skeletal group (i.e.,  $p\text{-C}_6\text{H}_4\text{—}$ ). But for clarity and convenience it seems justifiable to use  $p\text{-C}_6\text{H}_4\text{—}$  only for  $p$ -disubstituted heterocycles, and  $m\text{-C}_6\text{H}_4\text{—}$  for  $m$ -disubstituted ones. Available values of transmission factors for fundamental six- and five-membered heterocycles are listed in Table XXII.

## C. TRANSMISSION OF THE ELECTRONIC EFFECTS OF SUBSTITUENTS IN HETEROAROMATIC SYSTEMS

### 1. Six-Membered Heterocycles

a. *Pyridine Ring.* In the correlation analysis of the data on pyridine series the electronic effects are separated into inductive and resonance constituents only in rare cases. The single-parameter correlations available in the literature can only help to estimate the transmission of total substituent effects. But the conclusions are sometimes contradictory.

The dependences of the saponification rates of 5-substituted nicotines **41** and **42** and corresponding meta-substituted benzoates on the  $\sigma_m$  constants led to the conclusion that the electronic transmission in the benzene ring is higher than that in the pyridine (67NKZ1210; 70JCS(B)1063). At the same time, according to the data on the polarography for 5-substituted 3-nitropyridines (**43**), the transmission in the pyridine ring is higher than that in the benzene one (73AC(R)129). Certain doubts have been expressed as to the validity of the latter conclusion because of additional effects of interacting intermediate anion radicals and electrolyte cations in the electrochemical reduction of nitro compounds. Nevertheless, this conclusion agrees well with the values of transmission factors  $\gamma_I^{53}$  and  $\gamma_R^{53}$  calculated by Charton from the data on the ionization of 5-substituted nicotinic acids (**40**) (78MI1).

The kinetic data on the saponification of 5-substituted picolines (**58**) show the  $\rho$  value to be rather smaller than that for para-substituted methyl benzoates (70JCS(B)1063). But the closeness of the  $\rho$  values in correlation equations of the solvolysis rates of 5-substituted 2-( $\alpha$ -chloroethyl)pyridines and para-substituted  $\alpha$ -chloroethylbenzenes points to the same electronic transmission to para positions in the pyridine and benzene rings (72TL3893).

From comparisons of the single-substituent parameter equations for the two nitropyridine series **61** and **62**, the transmission of the total electronic effects of 6(2)-substituents to the para position were concluded to be higher than that for 5-substituents (73AC(R)135). The analysis of dual-substituent

TABLE XXII  
THE TRANSMISSION FACTORS IN HETEROCYCLES

<i>i,j</i> -Skeletal group (G) <sup>a</sup>	$\gamma$	$\gamma_1$	$\gamma_R$	Structural series
<b>1,3-Series</b>				
Six-membered ring				
3,1-Benzene	1.0	1.0	1.0	
2,4-Pyridine			~0.9	Y—G—C(Me) <sub>2</sub> L <sup>b</sup>
4,2-Pyridine	0.9			Y—G—COOMe <sup>c</sup>
5,3(3,5)-Pyridine	0.9			Y—G—COOMe <sup>c</sup>
	≥1.0			Y—G—NO <sub>2</sub> <sup>d</sup>
	1.15	1.19	1.02	Y—G—COOH <sup>e</sup>
			~1.0	Y—G—C(Me) <sub>2</sub> L <sup>b</sup>
2,4-Pyrimidine		1.3	1.6	Y—G—Cl <sup>f</sup>
		1.32	1.70	Y—G—NH <sub>2</sub> <sup>g</sup>
4,2-Pyrimidine		1.2	1.5	Y—G—Cl <sup>f</sup>
		1.23	1.84	Y—G—NH <sub>2</sub> <sup>g</sup>
6,4(4,6)-Pyrimidine		1.1	2.0	Y—G—Cl <sup>f</sup>
		1.20	2.09	Y—G—NH <sub>2</sub> <sup>g</sup>
4,2-s-Triazine		1.6	2.2	Y—G—NH <sub>2</sub> <sup>g</sup>
Five-membered ring				
4,2-Pyrrole	1.65	1.40	3.30	Y—G—COOH <sup>h,i</sup>
	1.43			Y—G—COOH <sup>j</sup>
5,3(2,4)-Pyrrole	1.16			Y—G—COOH <sup>j</sup>
4,2-Furan	~1.3			Y—G—CH(Me)L <sup>k</sup>
5,3(2,4)-Furan			3.1	Y—G—CH(Me)L <sup>l</sup>
4,2-Thiophene	~1.2			Y—G—CH(Me)L <sup>m</sup>
	0.97			Y—G—COOH <sup>i</sup>
5,3(2,4)-Thiophene	1.20			Y—G—COOH <sup>h</sup>
			1.9	Y—G—CH(Me)L <sup>l</sup>
3,5(5,3)-Pyrazole			1.7	Y—G—CH(Me)L <sup>b</sup>
4,2-Imidazole			3.8	Y—G—CH(Me)L <sup>b</sup>
<b>1,4-Series</b>				
Six-membered ring				
4,1-Benzene	1.0	1.0	1.0	
5,2(3,6)-Pyridine	≤1.0			Y—G—NO <sub>2</sub> <sup>n</sup>
	1.04			Y—G—CH(Me)L <sup>o</sup>
	0.9			Y—G—COOMe <sup>c</sup>
6,3(2,5)-Pyridine	1.1			Y—G—N=NPh <sup>p</sup>
	≥1.0			Y—G—NO <sub>2</sub> <sup>n,p</sup>
2,5-Pyrimidine		1.07	1.11	Y—G—NH <sub>2</sub> <sup>g</sup>
5,2-Pyrimidine	1.02(1.15)			Y—G—NHNH <sub>2</sub> <sup>r</sup>
	1.06(1.04)			Y—G—CONHNH <sub>2</sub> <sup>s</sup>
		1.03	1.00	Y—G—NH <sub>2</sub> <sup>g</sup>
Five-membered ring				
5,2-Pyrrole	1.65	1.62	2.08	Y—G—COOH <sup>e,h</sup>
5,2-Furan	1.40	1.37	1.50	Y—G—COOH <sup>e,h</sup>
	1.27		1.32	Y—G—CH(Me)L <sup>b,o</sup>
	1.17			Y—G—COOH <sup>i</sup>

(continued)

TABLE XXII (continued)

<i>i, j</i> -Skeletal group (G) <sup>a</sup>	$\gamma$	$\gamma_i$	$\gamma_R$	Structural series
5,2-Thiophene	1.10	1.24	1.13	Y—G—COOH <sup>e,h</sup>
	1.1–1.2			Y—G—CH(Me)L <sup>m</sup>
	1.21			Y—G—CONH <sub>2</sub> <sup>a</sup>
	1.12			Y—G—COOEt <sup>v</sup>
5,2-Selenophene	1.23	1.27	1.15	Y—G—COOH <sup>e,h</sup>
5,2-Tellurophene	1.20	1.18	1.24	Y—G—COOH <sup>e</sup>
5,2-Imidazole	0.97		1.01	Y—G—CH(Me)L <sup>b,w</sup>
2,5-Thiazole	1.05		0.94	Y—G—CH(Me)L <sup>b,o</sup>
5,2-Thiazole	1.15		1.11	Y—G—CH(Me)L <sup>b,o</sup>

<sup>a</sup> *i* and *j* refer to positions of substituent Y and reaction site, respectively.

<sup>b</sup> Solvolysis, 80% aq. EtOH, 25°C (76JOC776).

<sup>c</sup> Alkaline hydrolysis, 85% aq. MeOH, 25°C (70JCS(B)1063).

<sup>d</sup> Polarographic reduction, DMF (73AC(R)129).

<sup>e</sup> Acid ionization, 50% aq. EtOH, 25°C (78MI1).

<sup>f</sup> Piperidinolysis, *i*-octane, 60°C (72ZOR583).

<sup>g</sup> NH<sub>2</sub> chemical shift, DMSO (80MI1).

<sup>h</sup> Acid ionization, aq., 25°C (69T5815).

<sup>i</sup> Acid ionization, aq., 25°C (78MI1).

<sup>j</sup> Acid ionization, 50% aq. EtOH, 20°C (67DOK354).

<sup>k</sup> Solvolysis, 80% aq. EtOH, 25°C (69JOC1008).

<sup>l</sup> Solvolysis, 80% aq. EtOH, 75°C (76JOC776).

<sup>m</sup> Solvolysis, 80% aq. EtOH, 25°C (72JOC2615).

<sup>n</sup> Polarographic reduction, DMF (73AC(R)135).

<sup>o</sup> Solvolysis, 80% aq. EtOH, 25°C (72TL3893).

<sup>p</sup> Polarographic reduction, DMF (70MI2).

<sup>q</sup> Polarographic reduction, DMF (70MI1).

<sup>r</sup> NH<sub>2</sub> and NH chemical shifts, DMSO (85OR102).

<sup>s</sup> NH<sub>2</sub> and NH chemical shifts, DMSO (83OR85).

<sup>t</sup> Esterification, Ph<sub>2</sub>CN<sub>2</sub>, EtOH, 25°C (76AHC(20)1).

<sup>u</sup> Protonation, H<sub>2</sub>SO<sub>4</sub>, 25°C (80JCS(P2)1721).

<sup>v</sup> Alkaline hydrolysis, 62% aq. acetone, 25°C (65RTC1169).

<sup>w</sup> Solvolysis, 80% aq. EtOH, 45°C (73JOC3762).

parameter equations for the above series reveals an anisotropy of transmission as well as for the resonance effect ( $\rho_R^{25}/\rho_R^{52} = 1.2$ ) and the inductive effect of substituents ( $\rho_I^{25}/\rho_I^{52} = 1.1$ ) (77MI1).

One should be very careful in dealing with data on the ionization equilibrium and rates of decarboxylation of pyridinecarboxylic acids (71JOC454; 72JOC3938), since these acids may exist in zwitterionic forms and, for picolinic acids, with intramolecular H-bonds. It is precisely the latter that can account for the essential difference of the  $\rho$  values for ionization of 5-substituted

picolinic acids (**57**) ( $\rho = 2.31$ ), and 6-substituted nicotinic acids (**59**) ( $\rho = 1.60$ ) (67NKZ1210).

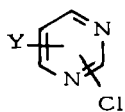
With other combinations of the positions of nitrogen heteroatom, substituent, and reaction site in the pyridine ring, the condition of their mutual conjugation is fulfilled and, as pointed out in Section IV,B, the influence of substituents is poorly described by single-substituent parameter correlations. Thus, data on the transmission of electronic effects in such structural series are still scarce. In the saponification of 6-substituted methyl picolinates (**50**) (70JCS(B)1065), and in the solvolysis of 6-substituted 2-( $\alpha$ -chloroisopropyl)-pyridines (**55**) (73JOC2660), the reaction rates do not follow the Hammett equations, since an essential change is found to have occurred in the ratio of the inductive and the resonance constituents of the total electronic effect of substituents, the latter effect increasing up to 44% as compared with 33% for the corresponding meta-disubstituted benzenes (73JOC3762). However, these data cannot be interpreted unequivocally since an increase in the transmission of the resonance effect may be accompanied by either a decrease or an increase in the transmission of inductive effect of substituents.

In the correlations discussed for all the structural series in reactions, except solvolysis, use was made of  $\sigma_1$ ,  $\sigma_R$ ,  $\sigma_m$ , and  $\sigma_p$  constants, the latter reaction involving the use of  $\sigma_m^+$  and  $\sigma_p^+$ .

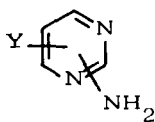
Summarizing the data presented in Table XXII, it can be concluded that:

1. The transmission of inductive effects through the pyridine ring is about the same as through the benzene ring; deviations do not exceed 10%.
2. The transmission of resonance effects from every even-numbered position is more or less increased and, as a consequence, anisotropy of the transmission is observed.

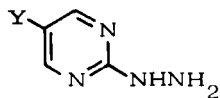
b. *Diazine and s-Triazine Rings.* Pyrimidines among all the azines best illustrate the problems of substituent effect transmission. Kinetic data were analyzed on the reaction of piperidino-dechlorination of chloropyrimidines (**75**) substituted at even ring positions in isooctane (72ZOR583). The  $\rho_1$  and  $\rho_R$  coefficients in dual-parameter equations for three pyrimidine series were compared with the  $\rho_1$  and  $\rho_R$  values calculated for meta-substituted chlorobenzenes to estimate the transmission factors for inductive and resonance effects (Table XXII).



( 75 )



( 76 )



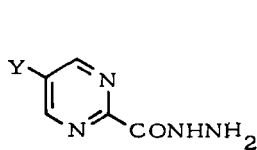
( 77 )



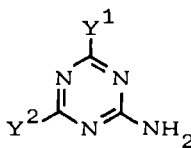
It is of interest to compare these results with those obtained for other pyrimidine series in which the reaction site is located in a side chain, e.g., in aminopyrimidines (76). For those the simplest operation is to determine the  $\text{NH}_2$  chemical shifts as a measure of their relative  $\text{NH}$  acidities.

The dual-substituent parameter equations obtained for five series of substituted 2-, 4-, and 5-aminopyrimidines (71IZV2173; 79KGS1683) and for two series of meta- and para-substituted anilines (79ZOR1737), have made it possible to calculate a large set of transmission factors. For the same series of aminopyrimidines there are data obtained from studies of substituent effects on equilibrium  $\text{N}-\text{H}$  acidities in DMSO (81ZOR312) and similar data for substituted anilines (77JOC1817). For the latter, however, the set of substituents is insufficient and there are no strong electron-releasing groups.

The values of the generalized transmission factor  $\gamma^{25}$  can be calculated from dependences found for the  $\text{NH}_2$  and  $\text{NH}$  chemical shifts in PMR spectra of 5-substituted 2-hydrazinopyrimidines (77) (85OR102) and 2-carboxyhydrazidopyrimidine (78) in DMSO (83OR85).



( 78 )



( 79 )

The transmission factors for *s*-triazine rings were calculated from the PMR spectra of 4(6)-substituted 2-amino-*s*-triazines (79) in DMSO (73ZOR1012).

The  $\sigma_1$  and  $\sigma_R$  (or  $\sigma_m$ ) constants were used as variable parameters in the above correlations for the meta series, and the  $\sigma_1$  and  $\sigma_R^-$  (or  $\sigma_p^-$ ) constants for the para series.

The following summary can be made:

1. The transmission of inductive effects through the pyrimidine ring is somewhat higher than that through the benzene ring.

2. But a more significant increase is observed in the transmission of resonance effects. The ability of the pyrimidine ring to transfer the resonance effect from one even-numbered to another even one (formally, to a meta position) is 1.5 to 2 times as high as that of the benzene ring. The 4- and 6-positions of the pyrimidine ring prove to be the most conjugated and in this respect are only slightly inferior to the para positions of the benzene ring.

3. For the 2- and 5-positions of the pyrimidine ring (formally para positions) an anisotropy of the transmission of resonance effects is observed.

Thus, the transmission from the 5-position of the ring to the 2-position is close to that of the same effect in the benzene ring, but it increases somewhat when transferred from the 2-position of the ring.

4. Conclusions 1 and 2 also refer to the transmission of electronic effects of substituents through the *s*-triazine ring.

## 2. Five-Membered Heterocycles

Although the situation is favorable for the use of single-substituent parameter correlations for five-membered heteroaromatic systems, the question of the transmission of electronic effects for them remains, to some extent, debatable. The large distortion of a benzenoid ring geometry occurring when a heteroatom (NH, O, S, Se, etc.) is substituted for the fragment  $-\text{CH}=\text{CH}-$  raises doubts as to whether it is correct to use the values of the Hammett constants for the heterocyclic series. In this connection, values of specific substituent constants have been calculated for the thiophene and the furan rings by the Dewar–Grisdale method (78JCS(P2)1232). Depending on which values of specific substituent constants or Hammett constants are used in correlations, quite different conclusions can be drawn concerning the transmission of electronic effects through heterocycles. Nevertheless, in most studies use was made of the conventional approach to transmission estimation involving Hammett constants.

Using the data on the ionization constants of the 5-substituted 2-carboxylic acids **30** and **31** (69T5815; 72JCS(P2)1738), the transmission of total electronic effects,  $\gamma^{52}$ , was shown to increase in the sequence benzene < thiophene < selenophene, tellurophene < furan < pyrrole (Table XXII).

The separation of inductive and resonance components made by Charton (78MI1) shows that the transmission of both components increases proportionally and the relative distribution of resonance remains nearly constant, increasing only for 2,5-disubstituted pyrroles.

An attempt was first made to attribute this sequence to changes in ring aromaticity, but later it was shown that there is no satisfactory correlation of transmission factors with aromaticity indexes (74AHC(17)255).

In spite of the limited data, there are good reasons to believe that the above sequence of increase in the transmission of substituent effects can be applied to the 2,4-disubstituted five-membered heterocycles (76JOC2350). In contrast to the 2,5-disubstituted heterocycles, however, the resonance effect transmission increases more dramatically. This increase is reflected in the value of the relative resonance effect contribution in various heteroaromatic systems: 3,1-benzene and 4,2-thiophene (33%) < 4,2-furan (39%) < 2,4-furan

(49%) < 4,2-imidazole (53%) (72JOC2623; 73JOC3762). The second peculiarity of the 2,4-disubstituted heterocycles is the anisotropy of resonance effect transmission.

#### D. INTERRELATIONSHIPS AMONG THE $\sigma$ VALUES FOR SUBSTITUTED PHENYL AND HETEROAROMATIC GROUPS

In Section IV,A, formalized Eqs. (33), (34), (38), and (39) are shown as permitting one to calculate the values of inductive and mesomeric constants for substituted phenyl and substituted pyrimidinyl groups on the basis of the respective contributions of unsubstituted groups, Ph or Pym, and substituent, Y (82DOK99).

Taken as a basis were Eqs. (33) and (34) for calculating the  $\sigma_I$  and  $\sigma_R^\circ$  values in which the terms  $a_{Ph}\sigma_I(Y)$  and  $b_{Ph}\sigma_R^\circ(Y)$  characterize quantitatively the contributions of inductive and mesomeric effects of substituents relative to the electronic effects of substituted phenyl groups.

Because the transmissions of the former and the latter effects through the benzene and pyrimidine systems are different (Section IV,C), the contributions of the inductive and mesomeric effects of the substituents to the electronic effects of the respectively substituted phenyl and pyrimidinyl groups have also been assumed to be different. The transmissions of electronic effects of substituents through heteroaromatic systems are numerically expressed by means of the transmission factors  $\gamma_I$  and  $\gamma_R$  (Section IV,B). The products  $\gamma_I a_{Ph}\sigma_I(Y)$  and  $\gamma_R b_{Ph}\sigma_R^\circ(Y)$  can therefore serve as numerical characteristics of the contributions of the inductive and mesomeric effects of the substituent Y to the electronic effects of a substituted heteroaromatic group. Thus, for substituted pyrimidinyl groups, Eqs. (38) and (39) take the form:

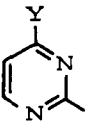
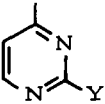
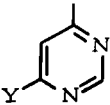
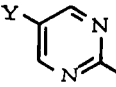
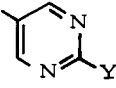
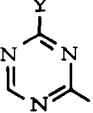
$$\sigma_I(\text{Pym-Y}) = \sigma_I(\text{Pym}) + \gamma_I a'_{Ph}\sigma_I(Y) + \gamma_R b'_{Ph}\sigma_R^\circ(Y) \quad (46)$$

$$\sigma_R^\circ(\text{Pym-Y}) = \sigma_R^\circ(\text{Pym}) + \gamma_I a''_{Ph}\sigma_I(Y) + \gamma_R b''_{Ph}\sigma_R^\circ(Y) \quad (47)$$

To verify Eqs. (46) and (47), use was made of the  $\gamma_I$  and  $\gamma_R$  values for the pyrimidine ring (Table XXII), and the values of the  $a_{Ph}$  and  $b_{Ph}$  coefficients calculated for substituted phenyl groups (Section IV,A,1). The parameters of Eqs. (46) and (47) are listed in Table XXIII. Table XXIV lists, as examples, the values of substituent constants found by  $^{13}\text{C}$  NMR and calculated with the aid of these equations for 2-, 4-, and 5-pyrimidinyl groups with electron-withdrawing (CN) and electron-releasing (OMe) substituents in various positions of a pyrimidine ring. The agreement between the calculated and the determined values is fairly satisfactory.

This approach was extended to *s*-triazines. The known values of the transmission factors for the *s*-triazine ring (Table XXII) and the  $\sigma$  values for some

TABLE XXIII  
PARAMETERS OF EQS. (46)–(49) FOR SUBSTITUTED  
PYRIMIDINYL AND *s*-TRIAZINYL GROUPS

Group	Equation	$\gamma_I \cdot a_{Ph}$	$\gamma_R \cdot b_{Ph}$
	46	0.20	0.26
	47	0.06	0.02
	46	0.21	0.24
	47	0.07	0.02
	46	0.19	0.29
	47	0.06	0.02
	46	0.12	0.20
	47	0.05	0.10
	46	0.13	0.22
	47	0.05	0.11
	48	0.26	0.31
	49	0.08	0.02

substituents (Cl, OMe, NMe<sub>2</sub>) have been introduced in Eqs. (48) and (49) for substituted *s*-triazinyl groups.

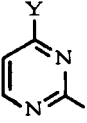
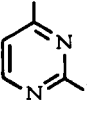
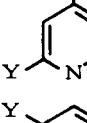
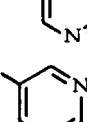
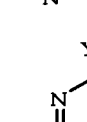

$$\sigma_I(\text{TrY}) = \sigma_I(\text{Tr}) + \gamma_I a'_{Ph} \sigma_I(Y) + \gamma_R b'_{Ph} \sigma_R^\circ(Y) \quad (48)$$

$$\sigma_R^\circ(\text{TrY}) = \sigma_R^\circ(\text{Tr}) + \gamma_I a''_{Ph} \sigma_I(Y) + \gamma_R b''_{Ph} \sigma_R^\circ(Y) \quad (49)$$

The calculated values of the constants for 4(6)-substituted 2-*s*-triazinyl groups agree fairly well with those found by the <sup>13</sup>C method (Table XXIV) (83TH1).

An opinion has been expressed as to the generality of this approach for it can be used to calculate  $\sigma$  values for composite heteroaromatic groups (82DOK99). Future investigations will outline the limits of its applicability. It remains unclear whether it is possible to estimate the electronic effects of polysubstituted heteroaromatic groups for which the additivity principle may fail.

TABLE XXIV  
 $\sigma$  VALUES CALCULATED FOR SOME SUBSTITUTED AZINYL GROUPS

Group	Substituent		Calculated		Determined	
	Y <sup>1</sup>	Y <sup>2</sup>	$\sigma_1$	$\sigma_R^\circ$	$\sigma_1$	$\sigma_R^\circ$
	OMe CN		-0.01 0.20	0.11 0.13	0.00 0.19	0.11 0.14
	OMe CN		0.16 0.36	0.10 0.13	0.17 0.35	0.10 0.13
	OMe CN		0.13 0.36	0.10 0.12	0.14 0.35	0.09 0.13
	OMe CN		-0.01 0.15	0.07 0.15	0.00 0.16	0.07 0.16
	OMe CN		0.24 0.41	-0.06 0.02	0.24 0.40	-0.06 0.01
	H Cl Cl Cl	OMe Cl OMe NMe <sub>2</sub>	0.13 0.30 0.18 0.11	0.20 0.25 0.24 0.23	0.15 0.32 0.18 0.13	0.20 0.24 0.22 0.22

## V. Conclusion

This article has shown that, despite the diversity of heterocyclic systems and the complications involved in developing general concepts, it is possible to find for heteroaromatic systems certain quantitative dependences permitting correlation of the data on the reactivity of aromatic and heteroaromatic compounds on the basis of well-developed approaches.

The approaches developed require determining a relatively small number of variables ( $\sigma_1$  and  $\sigma_R$  for the first member of a family and the transmission factors for a heteroaromatic system) and make it possible to calculate the  $\sigma$  values for substituted heterocyclic groups and thereby to estimate quantita-

tively the effect of such a composite fragment on reactivity and on a number of physical properties of heterocyclic compounds.

However, few parameters of this kind have so far been determined experimentally. Therefore, in heteroaromatic chemistry the quantitative investigation of reactivity remains a needed area of research. Also, being in a large measure of a formalized character, the equations obtained require a detailed analysis, which should reveal the peculiarities of transmission of electronic effects in various organic families, and allow understanding of the role played by the heteroatom in electronic effect transmission and the details of the subtle structure of interacting substituents. In this task, there is still an acute problem in quantifying the effect of solvent on the reactivity of heterocyclic compounds of different classes.

Despite the fact that a number of problems remain unsolved, the data reported in this article are expected to direct chemists interested in heterocycles to the large variety of work on the electronic effects of heteroaromatic groups.

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# Chemistry of Diazabicycloundecene (DBU) and Other Pyrimidoazepines

ISTVÁN HERMECZ

*CHINOIN Pharmaceutical and Chemical Works, Ltd., Research Center,  
1325 Budapest, Hungary*

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## I. Introduction

The general family of pyrimidoazepines encompasses seven distinct heterocyclic systems (1–7, see Fig. 1). Of these, only compounds containing the pyrimido[5,4-*c*]azepine ring system (6) are not known. The only available monograph on azepines refers to merely nine publications on these ring systems (84HC(1)236).

In this article the primary chemical literature up to the end of 1986 has been surveyed. *Chemical Abstracts* Subject and Chemical Substance Indexes up to and including Volume 104 have been searched. Throughout this article, the names and numbering style applied by *Chemical Abstracts* are used.

In the first part of the section on the pyrimido[1,2-*a*]azepines, the chemistry of 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepine (8) (generally called diazabicyclo[5.4.0]undec-7-ene, or DBU) is treated in a separate subsection, since DBU has proved to be a useful reagent in synthetic organic chemistry and an important catalyst in the synthesis of macromolecules. Since the appearance of two early reviews (72S591; 75M15), the applications of DBU have rapidly increased because of its favorable nonnucleophilic, yet strongly basic, properties. It can therefore be applied for the preparation of even relatively sensitive molecules. Following this, the synthesis, reactions, physicochemical properties, and briefly the applications of further pyrimido[1,2-*a*]azepine derivatives are discussed. The treatment of the chemistry of the other pyrimidoazepines (2–5 and 7) follows an essentially identical pattern to that for the pyrimido[1,2-*a*]azepines.

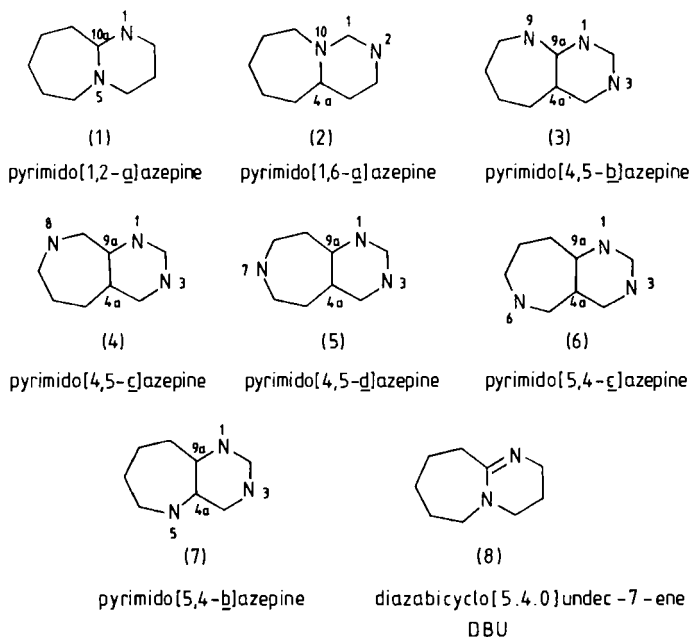


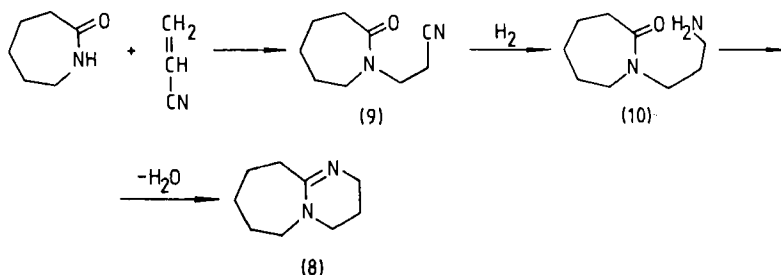
FIG. 1. Heterocyclic ring systems in pyrimidoazepines.

## II. Pyrimido[1,2-*a*]azepines (1)

### A. DIAZABICYCLO[5.4.0]UNDEC-7-ENE (8, DBU)

#### 1. Synthesis of DBU

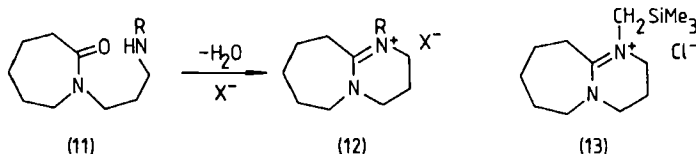
The synthesis of DBU starts from caprolactam and acrylonitrile. Caprolactam is reacted with acrylonitrile in the presence of potassium hydroxide at 80°C to give *N*-(2-cyanoethyl)caprolactam (**9**) (67AG53; 67AG(E)76; 69ZOR676; 70JAP(K)41226; 78HCA1050). Compound **9** is then hydrogenated in ethanol in the presence of sulfuric acid over PtO<sub>2</sub> catalyst (78HCA1050), or in a mixture of methanol and liquid ammonia at 100–120°C at 20–160 atm over Raney nickel (W-2) catalyst (67AG53; 67AG(E)76; 70JAP(K)41226; 71JAP(K)26516), to afford *N*-(3-aminopropyl)caprolactam (**10**) in 65–82% yield. After hydrogenation, **10** is cyclized (without isolation) to DBU by heating the reaction mixture at 150°C for 10 hr (71JAP(K)26516). Dehydration of **10** has also been carried out in boiling xylene in the presence of *p*-toluenesulfonic acid (67AG53; 67AG(E)76; 68FRP1491791; 69ZOR676; 70JAP(K)41226) under a water



condenser, or in *p*-cymene in the presence of  $Sb_2O_3$  or  $Bu_2SnO$  catalyst (73USP3761436), and proceeded in nearly quantitative yield. The ring closure of **10** was less effective under basic conditions (78HCA1050).

## 2. Reactions of DBU

DBU forms salts with inorganic and organic acids (e.g., 81BCJ790). DBU can be quaternized on N-1 with primary alkyl halides (67AG53; 67AG(E)76; 81HCA399; 84MI7). The quaternary salts **12** have also been prepared from caprolactam derivatives **11** by heating in xylene in the presence of *p*-toluenesulfonic acid under a water condenser (81HCA399).

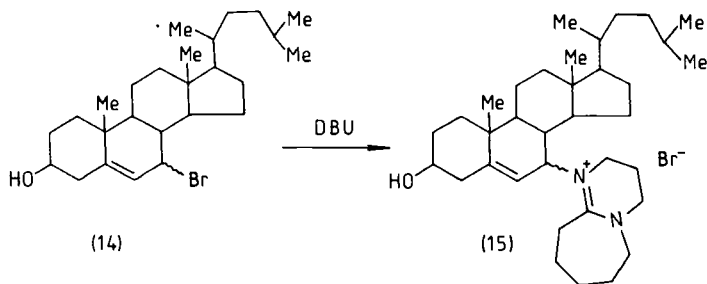


The hydrolysis of DBU and its quaternary salts (**12**) in aqueous methanolic potassium hydroxide gave the corresponding lactam (**10** or **11**) (81HCA399). Quaternization of DBU with trimethyl(chloromethyl)silane in dimethylformamide at ambient temperature gave **13** (82ZOB2055).

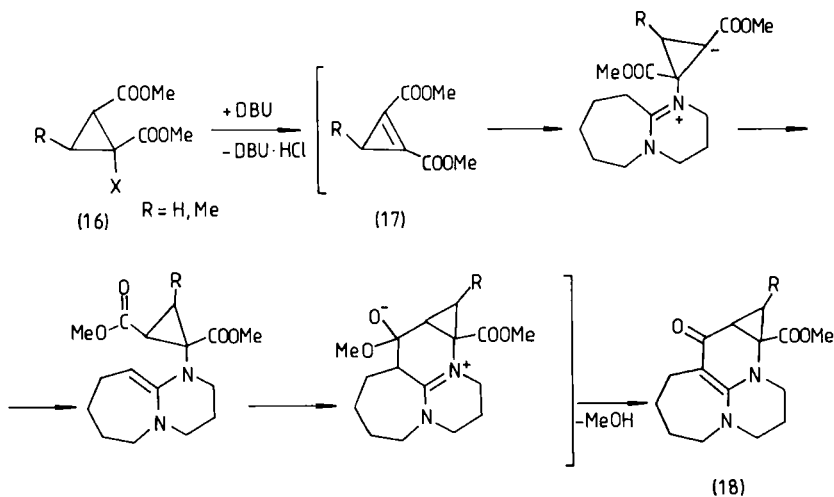
DBU has been quaternized with chloromethylated polystyrenes to give new ion-exchange resins (84BCJ1108). The chloride forms of these ion-exchange resins were effective as ion exchangers for bulky anions such as sulfate, oxalate, hexacyanoferrate(II) and (III), and tris(oxalato)ferrate(III). The adsorption of mercury(II) and copper(II) chlorides and iodides on these resins was also investigated.

The reaction of bromosteroid **14** and DBU in refluxing hexane under a nitrogen atmosphere gave an isomeric mixture of quaternary ammonium steroids (**15**) (71USP3553211).

Tetracyclic compounds **18** were obtained, together with the DBU hydrohalide salt, in the reaction of dimethyl 1-halocyclopropane-1,2-dicarboxylates

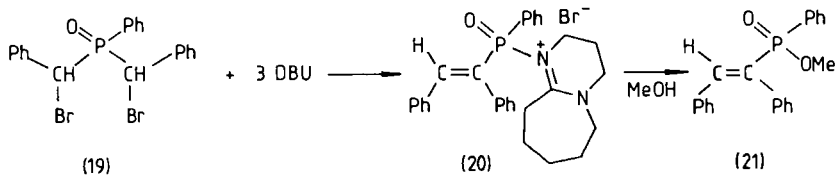


(16) with 3 mol equiv. of DBU in ethyl acetate or in furan at room temperature for 7 days (81JOC1016). It was assumed that dehydrohalogenation of **16** occurred in the first step. The resulting cyclopropenedicarboxylate (**17**) then reacted further with DBU (Scheme 1).



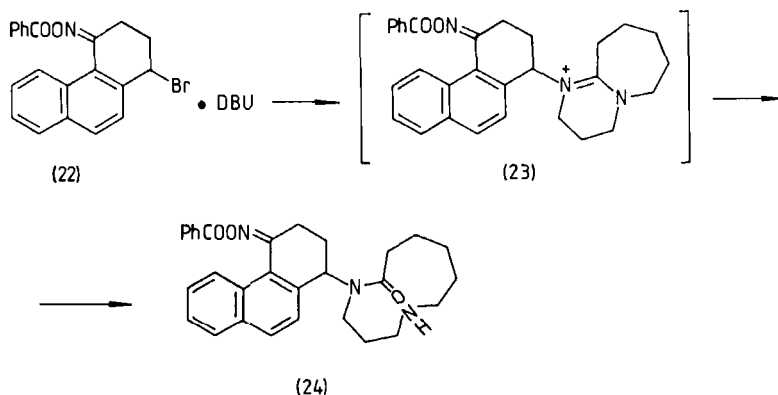
SCHEME 1

Treatment of bis( $\alpha$ -bromobenzyl)phenylphosphane oxide (**19**) with 3 mol equiv. of DBU in benzene furnished an (*E*)-1,2-diphenylvinylphosphorus derivative (**20**). Solvolysis of **20** in methanol gave (*E*)-1,2-diphenylvinylphenylphosphinic acid methyl ester (**21**) (79CC390).

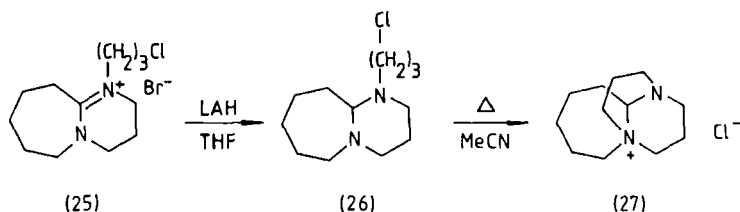




Besides the expected dehydrobromination, the formation of **24** in low yield also occurred via the quaternary salt **23** in the reaction of **22** with DBU in methylene bromide at ambient temperature (75MI2; 75T701; 82T551). From the reaction mixture, 13 additional products could be isolated in 0.7–24.7% yield.

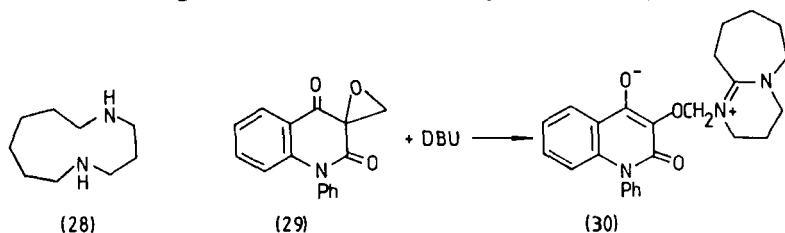


The quaternary bromide **25**, obtained from DBU and 3-bromo-1-chloropropane in diethyl ether, was reduced with lithium aluminum hydride (LAH) in tetrahydrofuran (THF) at ambient temperature to give a perhydro bicycle (**26**), which was then cyclized in refluxing acetonitrile to a tricyclic salt (**27**) (82TL1121).

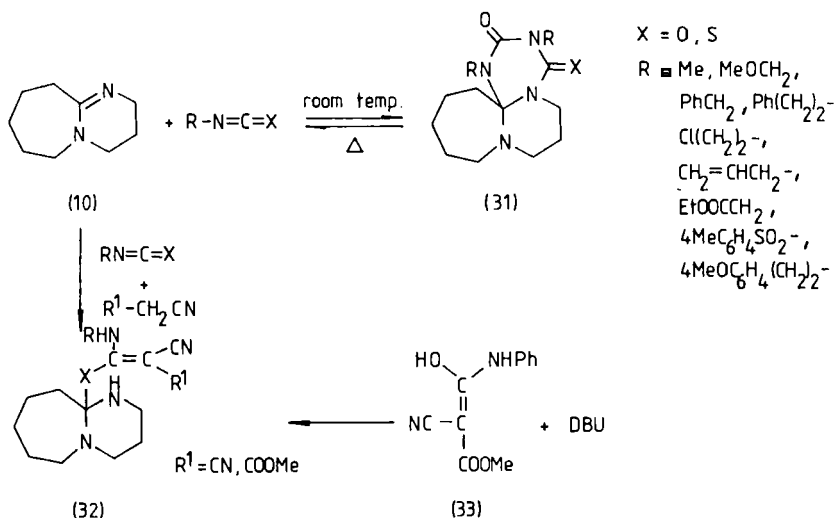


Reduction of DBU with excess diisobutylaluminum hydride in refluxing toluene for 7 hr gave an 11-membered cyclic diamine (**28**) in 96% yield (81JA4186).

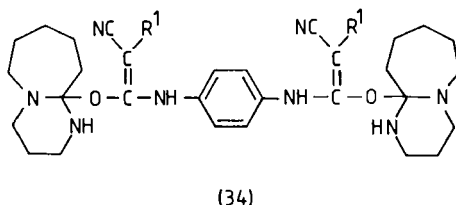
On reacting with DBU at ambient temperature for 3 days, the spiro-quinolinedione **29** gave the betaine **30** in 74% yield (78ZN(B)429).



Reaction of DBU with 2 mol equiv. of isocyanates or isothiocyanates afforded tricyclic adducts **31** (76IJC(B)763; 78GEP2640964; 81MI1). On heating, **31** decomposed to the starting materials (81MI1).

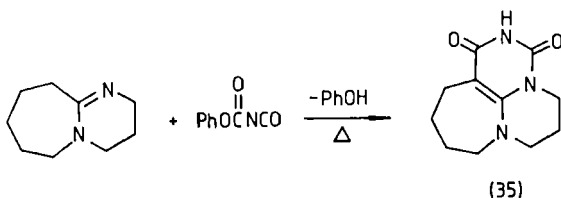


Reactions of DBU and isocyanates or isothiocyanates in the presence of cyanoacetate or malononitrile in dimethylformamide gave **32** (78GEP2640965). Compound **32** (X = O, R = Ph, R<sup>1</sup> = COOMe) was obtained in the reaction of DBU with 2-cyano-3-hydroxy-3-(phenylamino)acrylate (**33**). 1,4-Diisocyanatobenzene yielded the bis derivative **34**.

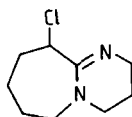


The reaction between DBU and phoxycarbonyl isocyanate afforded a 2,3a,6a-triazacyclohepta[*d,e*]naphthalene derivative (**35**) (73GEP2126148).

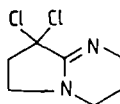
DBU undergoes a slow deuterium exchange with CDCl<sub>3</sub> to give a product deuterated in position 10 (81CC998).



In carbon tetrachloride at 40–45°C under a nitrogen atmosphere in darkness, DBU gave the 10-chloro derivative (**36**) (81CC998; 84JHC583). It was suggested that chlorination was initiated by an electron transfer from DBU to carbon tetrachloride in a primarily formed weak charge-transfer complex, followed by decomposition into a chloride ion and a trichloromethyl radical (81CC998). This radical abstracted a hydrogen from position 10 of DBU within the solvent cage, yielding chloroform and an iminium salt, which reacted further to give the 10-chloro compound (**36**). Under similar conditions, the five-membered homologue, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), afforded the 9,9-dichloro derivative (**37**) (81CC998).

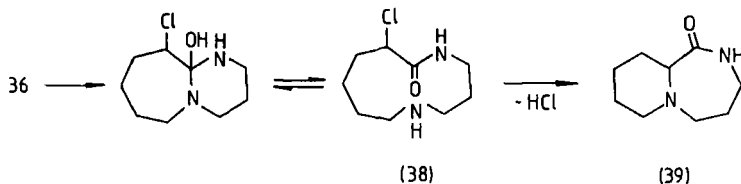


(36)



(37)

Hydrolysis of the 10-chloro derivative **36** in 0.5 *M* sodium hydroxide solution at 50°C for 6 hr gave the 2,6-diazabicyclo[5.4.0]undecan-1-one (**39**), probably via the 11-membered azalactam (**38**) through intramolecular alkylation (84JHC583).

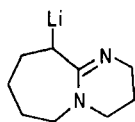


(38)

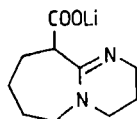
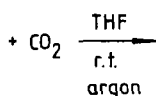
(39)

From the lithium derivative **40**, prepared from DBU and butyllithium under an inert atmosphere (83CB1866; 84MI7), carboxylate **41** was obtained with gaseous carbon dioxide in tetrahydrofuran at room temperature (83CB1866). Compound **41** was isolable and stable for several hours at room temperature under an inert atmosphere, and proved to be a facile trans-carboxylation agent.

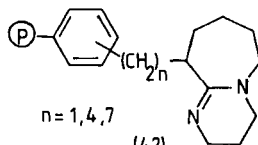
The reaction of lithiated DBU **40** with chloromethylated or  $\omega$ -bromoalkylated polystyrene resins resulted in polystyrene-supported DBU



(40)



(41)

 $n = 1, 4, 7$ 

(42)

(PDBU) (42) (84MI7). PDBUs are effective as reagents for dehydrohalogenation and esterification.

Some further reactions are to be found in Section II,A,4,c.

### 3. Physicochemical Properties of DBU

DBU is a liquid at room temperature and atmospheric pressure. Its dipole moment in benzene is 3.41 D (72BSF3743). Table I gives  $pK_a$  values for DBU, together with those of some other nonnucleophilic bases.

The following boiling points have been reported for DBU: 97–98°C/3 mm (69FRP1542058; 70JAP(K)41226); 100°C/4 mm (71JAP(K)26516); 127–128°C/14 mm (68FRP1491791; 79JMC237); 135–140°C/40 mm (69ZOR676). The following refractive indices and relative densities are mentioned in the literature:  $n_D^{20} = 1.5186$  (69ZOR676) and 1.5209 (69FRP1542058; 70JAP(K)41226);  $d^{20} = 1.030$  (69ZOR676) and 1.0378 (69FRF1542058; 70JAP(K)41226).

### 4. Applications of DBU in Syntheses

a. *Applications of DBU in Reduction and Oxidation Reactions.* Nitrobenzenes, nitrosobenzene, and phenylhydroxylamine could be reduced

TABLE I  
 $pK_a$  VALUES OF DBU AND SOME OTHER NONNUCLEOPHILIC BASES

Base	$pK_a$	Base	$pK_a$
DBU	11.5 <sup>a</sup>	NEt( <i>i</i> -Pr) <sub>2</sub>	10.50 <sup>g</sup>
	11.6 <sup>b</sup>	N-Ethylpiperidine	10.40 <sup>f</sup>
	12.9 <sup>c</sup>	DABCO <sup>h</sup>	8.70 <sup>f</sup>
	13.4 <sup>d</sup>	N(CH <sub>2</sub> CH <sub>2</sub> OH) <sub>3</sub>	7.77 <sup>f</sup>
1,8-Bis(dimethylaminonaphthalene)	12.34 <sup>e</sup>	N-Methylmorpholine	7.40 <sup>i</sup>
(Proton Sponge)		2,6-Dimethylpyridine	6.80 <sup>f</sup>
NEt <sub>3</sub>	10.87 <sup>f</sup>	<i>N,N</i> -Dimethylaniline	5.15 <sup>f</sup>

<sup>a</sup> 75MI5; 83CL1837; 83H1541.

<sup>b</sup> 84TL2183.

<sup>c</sup> In 1 *M* aqueous solution 70JAP(K)41226.

<sup>d</sup> In 10% aqueous solution 83MIA.

<sup>e</sup> 68CC723.

<sup>f</sup> 83H1541.

<sup>g</sup> 74MI1.

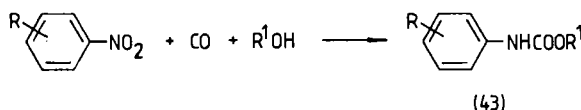
<sup>h</sup> 1,4-Diazabicyclo[2.2.2]octane.

<sup>i</sup> 75MI5.

with hydrogen to anilines in the presence of DBU and metallic selenium (75CC42). A DBU salt of hydrogen selenide was suggested to be the reducing agent.

In the presence of  $\text{PtCl}_2(\text{PPh})_3$ ,  $\text{SnCl}_4$ , ethanol, and DBU at  $180^\circ\text{C}$  for 4 hr under an initial pressure of  $60 \text{ kg cm}^{-2}$  carbon monoxide, the reductive N-carbonylation of nitrobenzene yielded ethyl phenylcarbamate and aniline in 62 and 16% yields, respectively (83BCJ3343).

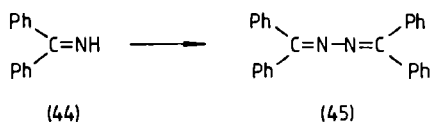
The reaction of nitrobenzenes with an aliphatic, araliphatic, or cycloaliphatic alcohol and carbon monoxide in the presence of a DBU-containing catalyst mixture yielded aromatic urethanes **43** (77GEP2614101; 80GEP2808980; 80GEP2808990; 80GEP2838754).



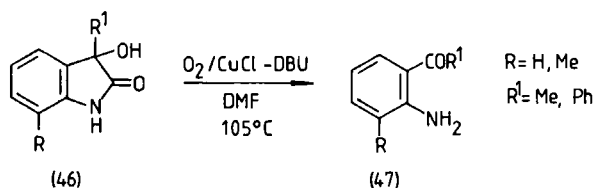
Aromatic urethanes and dialkyl carbonates were simultaneously prepared by the reaction of aromatic nitro compounds with alcohols and carbon monoxide over a catalyst mixture containing DBU (82JAP(K)32251).

Urethanes were also obtained from a mixture of aromatic primary amine and alcohol by oxidative catalytic carbonylation with carbon monoxide in the presence of a catalyst mixture containing DBU (81GEP2908250; 83EUP83096).

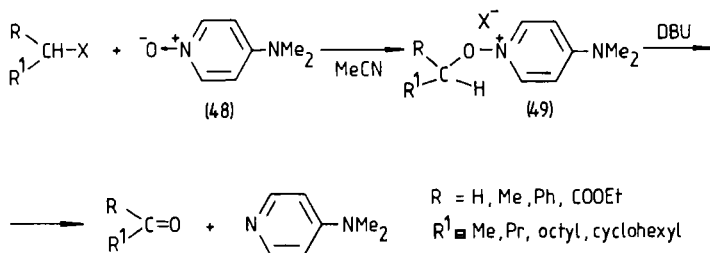
Oxidative coupling of diphenylmethanimine (**44**) in the presence of DBU and copper(I) chloride afforded benzophenone azine (**45**) (77CL981; 79JAP(K)24859). The best yield was achieved in dioxane or tetrahydrofuran.



2-Acylanilines **47** were prepared in moderate yields from 3-hydroxy-2-indolinones **46** by air oxidation with a copper(I) chloride–DBU catalyst (84JAP(K)134757).

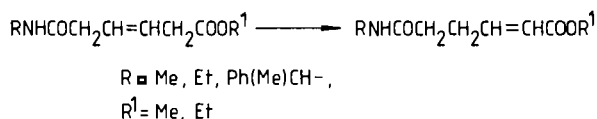


Primary and secondary alkyl chlorides and bromides were oxidized to aldehydes and ketones in high yields with 4-dimethylaminopyridine *N*-oxide (**48**) in the presence or absence of DBU in acetonitrile. In the second step, DBU proved to be the most useful base for the deprotonation of compounds **49** (81BCJ2221).



Alkylenyl glycol esters were obtained by the oxidation of the respective olefins with oxygen in carboxylic acids containing a soluble palladium salt and nitrogen bases (e.g., DBU) (75JAP(K)24208).

*b. Applications of DBU in Isomerization, Dimerization, and Rearrangement Reactions.* The isomerization of 5-carbamoyl-3-pentenoates in the presence of DBU in refluxing tetrahydrofuran gave isomeric 2-pentenoates in high yields (77JAP(K)133917).

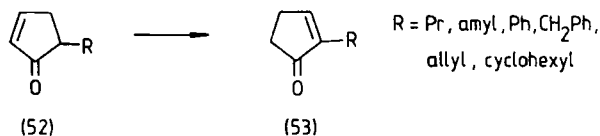


At 100°C, methyl and ethyl 3-pentenoates were isomerized with DBU to the corresponding 2-pentenoates (81JAP(K)55345).

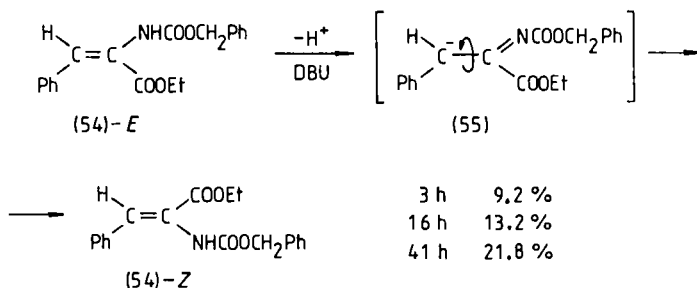
The equilibration of either 5-methyl-4-hexen-2-one or *trans*-5-methyl-3-hexen-2-one in *tert*-butanol in the presence of DBU at 25°C gave a 2.5:1 mixture of **50** and **51** (83JOC584).



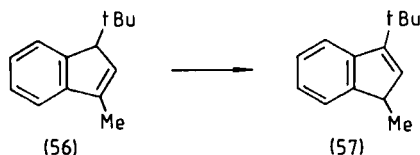
When 4-substituted 2-cyclopentenones **52** were heated at 110–150°C in the presence of DBU or its salts, 2-substituted 2-cyclopentanones **53** were formed in almost quantitative yields (85GEP3412713).



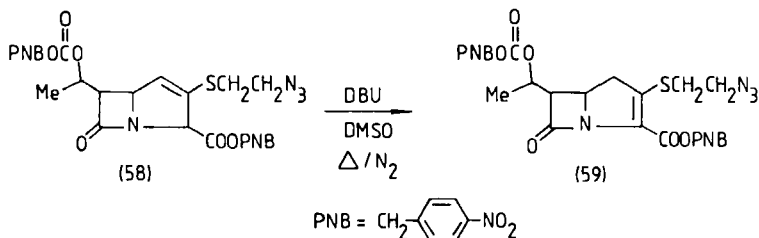
A slow isomerization of the (*E*)-isomer of **54** was observed in  $\text{CDCl}_3$  at  $25^\circ\text{C}$  in the presence of DBU (81JOC2667). Because the *N*-methyl derivative of (*E*)-**54** did not isomerize during 48 hr, a deprotonation mechanism was suggested for the isomerization. In the first step the amide proton was abstracted to give a delocalized anion (**55**), which could rotate about the carbon-carbon single bond to yield the (*Z*)-isomer of **54**.



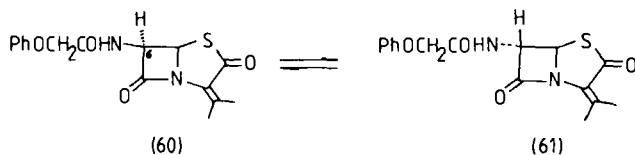
Ahlberg and Ladhar studied the 1,3-proton transfer reaction of (+)-3-*tert*-butyl-1-methylindene (**56**) with DBU in benzene and dimethyl sulfoxide to give (–)-1-*tert*-butyl-3-methylindene (**57**) (73CS31). In benzene the isomerization was highly stereospecific (99.996%), but in dimethyl sulfoxide it was not. In the latter case, racemization also occurred.



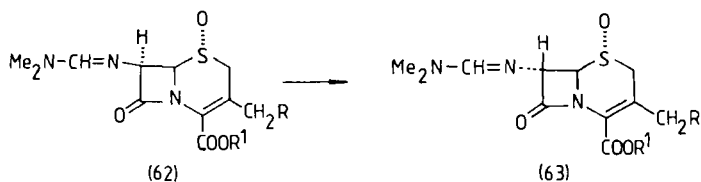
In the presence of DBU under a nitrogen atmosphere, compound **58** was isomerized to the thienamycin derivative **59** on heating (77GEP2652676).



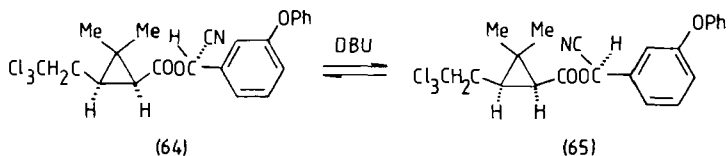
In the presence of DBU in  $\text{CDCl}_3$  at  $22^\circ\text{C}$ , the epimerization of phenoxymethylanhydronicillin (**60**) at C-6 gave an equilibrium mixture of anhydronicillin (**60**) and 6-epianhydronicillin (**61**) in a 60:40 ratio (83JA1006). Under the same conditions, the epimerization of benzylpenicillin did not occur.



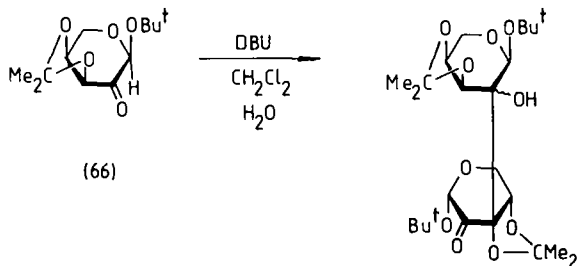
$7\beta$ -(Dimethylamino)methyleneamino]-3-cephem ester 1-oxides (**62**) were epimerized to the  $7\alpha$ -isomers (**63**) with DBU in dichloromethane at  $0^\circ\text{C}$  (82USP4334065).



Racemic isomers of  $\alpha$ -cyano-3-phenoxybenzyl *cis*-2,2-dimethyl-3-(2,2,2-trichloroethyl)cyclopropanecarboxylate (**64**) were isomerized to **65** at the  $\alpha$ -position by heating in *i*-propanol in the presence of DBU (81GEP3008986).

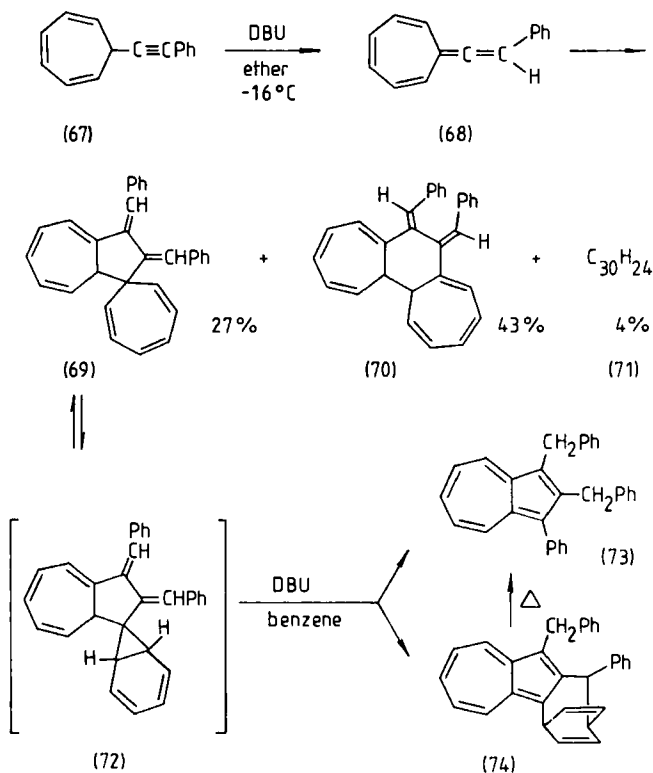


When pyranosidule (**66**) was refluxed for 1 hr in the presence of water and DBU in dichloromethane, it gave a dimeric product in 70% yield (76MI2). When triethylamine was used instead of DBU, no reaction occurred.





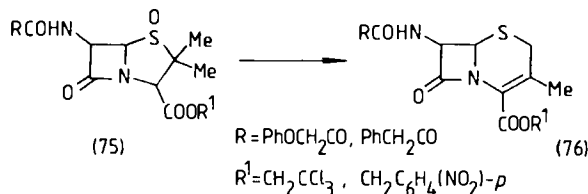
Allene **68**, formed *in situ* from 1-(2,4,6-cycloheptatrien-1-yl)-2-phenylacetylene (**67**) in the presence of DBU in diethyl ether, underwent dimerization to give compounds **69**, **70**, and **71** in 27, 43, and 4% yields, respectively (79CL171). Heating of compound **69** with DBU in benzene afforded a 2:1 isomeric mixture of azulenes **73** and **74** in 90% yield. The formation of the azulene derivatives (**73** and **74**) probably proceeds via the norcaradiene tautomer (**72**) of **69** (Scheme 2).



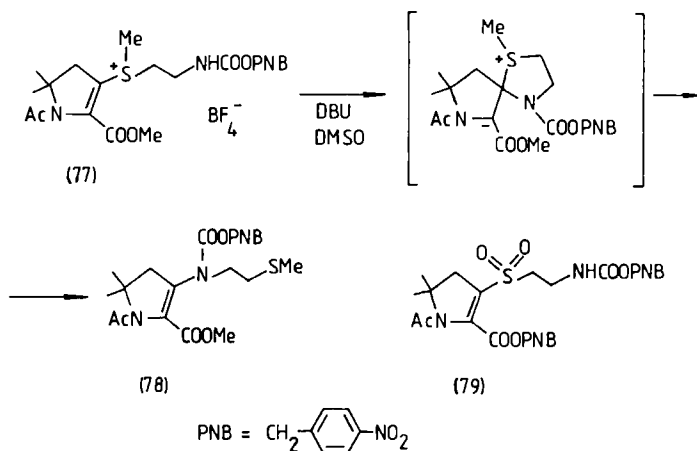
SCHEME 2

7-Acylamino-3-deacetoxycephalosporinic acid derivatives (**76**) were prepared in high yields by the rearrangement of penicillin 1-oxides (**75**) in the presence of DBU and *p*-toluenesulfonic acid monohydrate at reflux temperature (76JAP(K)56483).

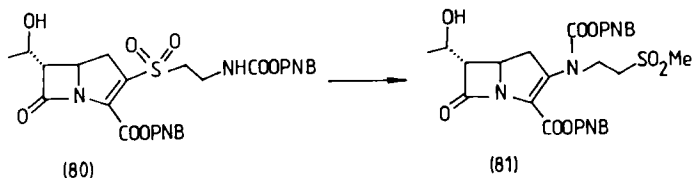
Treatment of the sulfonium salt (**77**) with 1.0 mol equiv. of DBU in dimethyl sulfoxide at ambient temperature afforded the 3-amino-2-pyrroline



**78** in 50% yield in a Smiles rearrangement (85JOC1996). The similar reaction of the sulfone **79** occurred only when sodium hydride was applied instead of DBU.

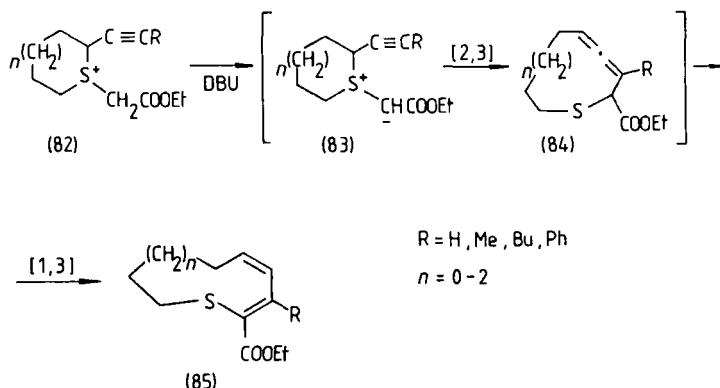


However, when the carbapen-2-am-3-carboxylate **80** was treated with 1.0 mol equiv. of DBU in dimethyl sulfoxide or in dimethylformamide in the presence of a slight excess of methyl iodide at room temperature for 15 min, the rearranged product **81** was obtained in 14% yield (85JOC1996). If sodium hydride was used as base in the latter reaction, the  $\beta$ -lactam ring underwent decomposition.

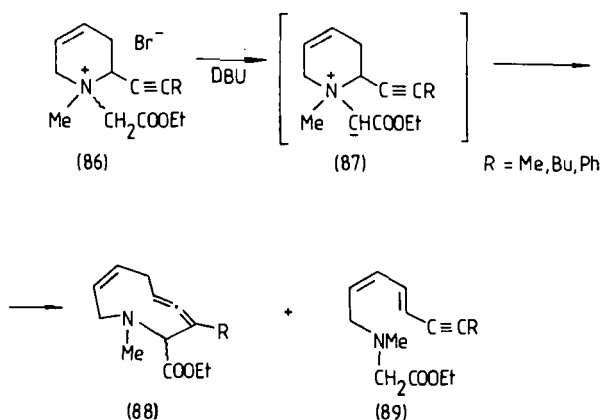


On the action of DBU in acetonitrile at ambient temperature, 2-ethynylthiacycloalkanes **82** yielded ring-expanded products **85** (82H2147). In the first

step, *S*-ylides **83** were probably formed, which then underwent a [2,3]-rearrangement to give allenic intermediates **84**. Finally, the latter could have undergone a 1,3-hydrogen shift to yield compounds **85**.

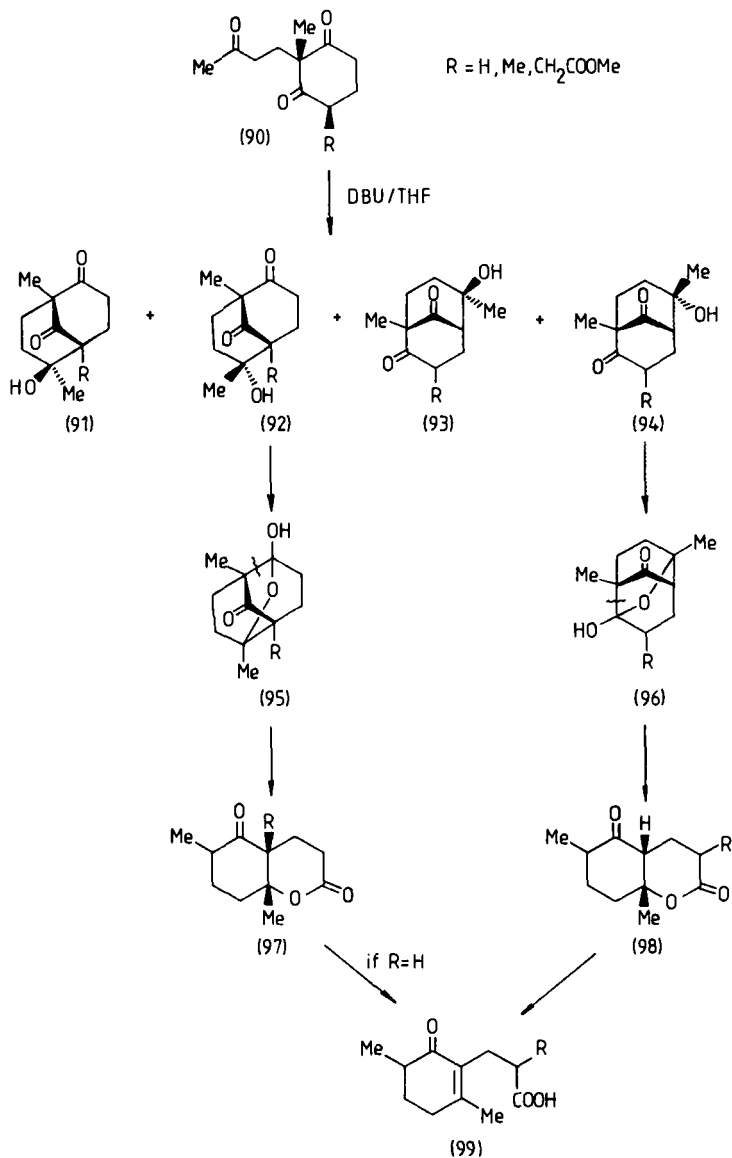


Treatment of 1-ethoxycarbonylmethyl-1,2,5,6-tetrahydropyridinium bromides **86** with DBU in tetrahydrofuran at ambient temperature gave *N*-ylides **87**, which under the reaction conditions applied isomerized to allenic compounds **88** and ring-opened products **89** (84CPB4600). Allenic compounds **88** were formed in a [2,3]-sigmatropic rearrangement, while ring-opened products **89** were obtained in a Hofmann elimination.



Treatment of trione **90** with DBU in tetrahydrofuran at room temperature gave a mixture of the cyclohexenone acid **99** ( $R = H$ ), the bridged derivative **91** ( $R = H$ ), and 2-methylcyclohexane-1,3-dione in 46, 15, and 15% yields, respectively ( $R = H$ ); a mixture of the cyclohexenone acid **99** ( $R = Me$ ), the bicyclic lactone **97** ( $R = Me$ ), and the bridged derivatives **91** and **93** ( $R = Me$ ) in 23, 35, 11, and 15% yields, respectively ( $R = Me$ ); and a mixture

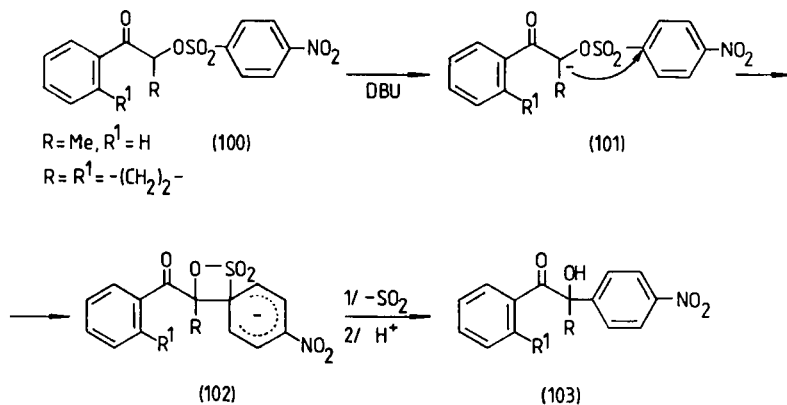
of the cyclohexenone acid **99** ( $R = \text{CH}_2\text{COOMe}$ ) and the bicyclic lactone **97** ( $R = \text{CH}_2\text{COOMe}$ ) in 11 and 49% yields, respectively ( $R = \text{CH}_2\text{COOMe}$ ) (85JOC69). The following reaction pathway was proposed for the formation of the above derivatives (Scheme 3). Aldol cyclization of the triketones **90**



SCHEME 3

might yield four types of bridged derivatives, presumably with both endo (**92** and **94**) and exo (**91** and **93**) stereochemistry. When the hydroxy group was in the endo position, rearrangement to cis-fused bicyclic lactones **97** and **98** could have occurred via the hemiketals **95** and **96**. Ring opening of lactones **98** would result in the formation of the cyclohexenone acids **99**, which were isolated as the methyl esters after treatment with diazomethane.

Hoffman *et al.* investigated the reactions of  $\alpha$ -nosyl ketones with different nucleophiles (86JOC51). When the nonnucleophilic DBU was applied as base, unique rearrangements of  $\alpha$ -nosyl ketones (**100**) were observed. Reaction of **100** with DBU in benzene gave  $\alpha$ -hydroxy- $\alpha$ -(4-nitrophenyl) ketones **103** via enolates **101** and presumed four-membered ring intermediates **102**. The latter (**102**) open to afford sulfur dioxide and **103**. The same products were also obtained with DBN.

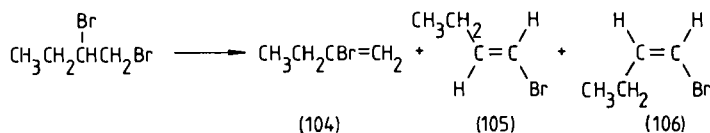


An  $\epsilon$ -caprolactam-tin(IV) chloride complex was prepared in nearly quantitative yield from the cyclohexanone oxime-tin(IV) chloride complex in the presence of sulfur trioxide and DBU in 1,2-dichloroethane at  $60^\circ\text{C}$  (74USP3828028).

*c. Applications of DBU in Elimination Reactions.* Due to its weak nucleophilic but strong basic properties, DBU has proved to be a versatile dehydrohalogenation agent for the conversion of secondary and tertiary alkyl halides and vicinal dihalogen derivatives under mild conditions to alkenes and alkynes (72S591; 75MI5; 82MI3).

In general, primary alkyl halides do not give the corresponding 1-alkenes. Instead, quaternary salts are formed (see Section II.A,2). However, if the  $\beta$ -carbon of the primary alkyl halides contains an activating atom or group (e.g., an aryl group or a further halogen atom), elimination takes place.

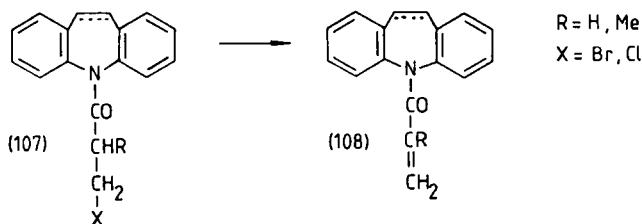
Thus, 1,2-dibromobutane gave a mixture of 2-bromo-1-butene (**104**) and a 1:1 mixture of (*E*)- and (*Z*)-1-bromo-1-butene (**105** and **106**) (82JOC1944).



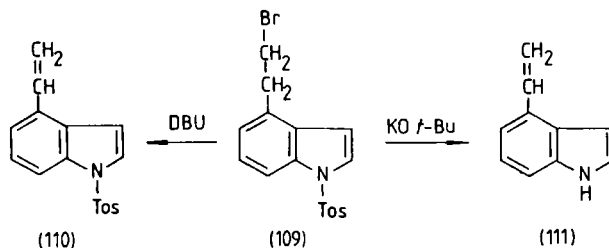
The reaction of phenethyl bromide with excess DBU in refluxing benzene afforded styrene in 60% yield (78BCJ2401).

When 2% 1,2,2-trichloroethane in helium was passed at 250 m hr<sup>-1</sup> through a tubular reactor packed with silica gel containing 5.6% DBU hydrochloride at 250°C, a 9:1 mixture of 1,1- and 1,2-dichloroethylene resulted (81JAP(K)40621).

Dibenzazepines **107** underwent dehydrohalogenation with DBU in dimethyl sulfoxide at 80–90°C to yield **108** (71GEP2104557; 78MI2).

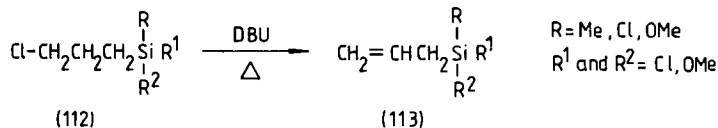


Treatment of 1-tosyl-4-(2-bromoethyl)indole (**109**) with DBU in refluxing benzene gave 1-tosyl-4-vinylindole (**110**) in 88% yield (78LA1702). If dehydrobromination of **109** was carried out with potassium *tert*-butoxide, detosylation also occurred to give 4-vinylindole (**111**).



Allylsilanes **113** were prepared from 3-chloropropylsilanes **112** with DBU at 180–190°C (78JAP(K)135934).

Wolff *et al.* showed that 1-alkenes can be obtained from primary alkyl iodides that contain a disubstituted  $\beta$ -carbon atom by treatment with 1.5 mol

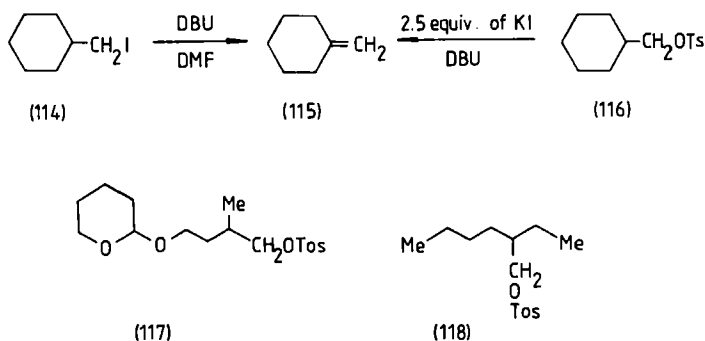


Eq. of DBN or DBU at 80–90°C (82JOC4358). The reaction of cyclohexylmethyl iodide (114) with DBU afforded methylenecyclohexane (115) in 60% yield in dimethylformamide.

Similar treatment of tosylates 116–118 did not give the corresponding 1-alkenes, but in the presence of 2.5 mol equiv. of potassium iodide, dehydroiodination took place. Double bond isomerization was not observed during the elimination processes. With DBU in the presence of potassium iodide in dimethylformamide, 1-octyl tosylate furnished 1-octene in only 5% yield.

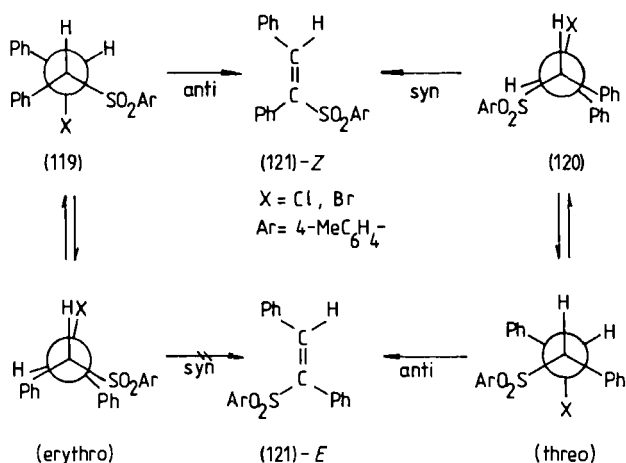
The stereochemistry of dehydrohalogenation with DBU has been studied by several authors. Wolkoff (82JOC1944) studied in detail the stereochemical consequences of dehydrohalogenation of secondary and tertiary alkyl and cycloalkyl halides with DBU. A comparison of the product distributions obtained in the elimination reactions of alkyl halides with DBU, with weak bases, and with anionic bases indicated that the elimination reactions with DBU very probably follow an E2C-like mechanism.

The achieved regioselectivity (the formation of 2-alkenes versus that of 1-alkenes) and stereoselectivity [the ratio of (*E*) and (*Z*) geometric isomers for 2-alkenes] were equal to or better than the results reported earlier with other bases.



The best regio- and stereoselectivities were obtained from 2-iodoalkanes, and decreased in the sequence 2-bromo- > 2-chloro- > 2-tosyloxyalkenes. Both the regio- and the stereoselectivities were lower when hydrogen halide elimination was performed with DBN than when DBU was used (82JOC1944). In general, the application of DBU gave higher yields than those with DBN (67AG53; 67AG(E)76; 69GEP1279679).

Fiandanese *et al.* investigated the dehydrohalogenation of *threo*- and *erythro*-1-chloro- and 1-bromo-1,2-diphenyl-2-(*p*-tolylsulfonyl)ethanes (**119** and **120**) with different agents, including DBU (75JCS(P2)221). In all cases, only (*Z*)-**121** was formed from *erythro*-**119** by anti elimination, whereas the ratio of the anti and syn eliminations for *threo*-**120**, giving an (*E*)-(Z) isomeric mixture of **121**, was strongly dependent on the reaction conditions. When DBU was used, the syn elimination increased when the solvent was changed from nitromethane to benzene, or when the chloro derivative (**120**, X = Cl) was applied instead of the bromo compound (**120**, X = Br).



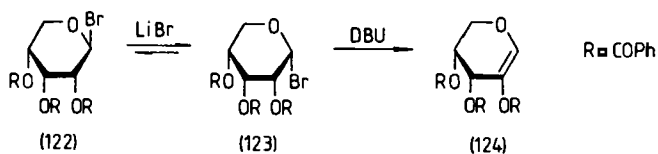
2-Hydroxyglycols were prepared from polyacylglycosyl bromides containing the bromine atom and the 2-acyloxy group in the *cis* positions by reaction with DBU in dimethylformamide at 0–30°C (71MI1; 72MI2). The yields decreased when benzene was applied as solvent instead of dimethylformamide. Reaction without a solvent, or elevation of the reaction temperature, resulted in extensive decomposition. Glycosyl chlorides proved not to be reactive enough with DBU to give 2-hydroxyglycols.

For the hydrogen bromide elimination an E2 mechanism was considered, as tetra-*O*-acetyl- $\alpha$ -D-mannopyranosyl bromide and tri-*O*-acetyl- $\alpha$ -D-rhamno-pyranosyl bromide, which contain the bromine atom and 2-acetoxy group in the *trans* positions, could not be dehydrobrominated.

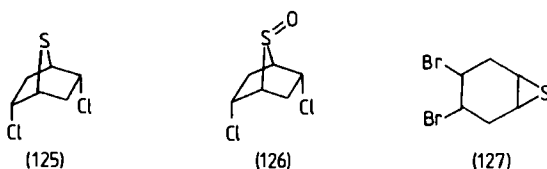
Hughes successfully extended the above method of Rao and Lerner to the dehydrobromination of the 1,2-*trans*-polyacylglycosyl bromides (72MI3). When the  $\beta$ -bromide **122** was reacted first with lithium bromide–hexamethylphosphortriamide, and then with DBU in dimethylformamide at ambient temperature, the dehydrobrominated product **124** was obtained. In the first



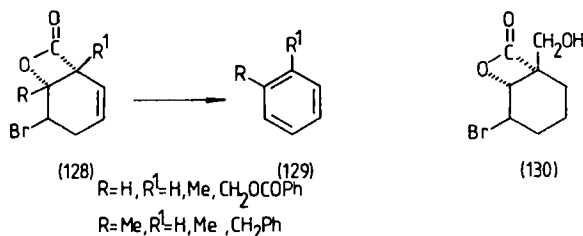
step, anomerization of the  $\beta$ -bromide (122) by the bromide ion occurred, to give the  $\alpha$ -bromide (123), which was then involved in the elimination reaction.



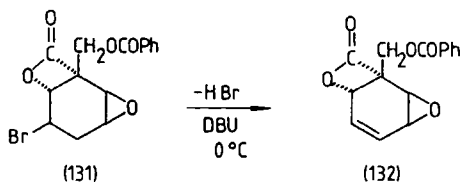
The treatment of 2,5-bis-*endo*-dichloro-7-thiabicyclo[2.2.1]heptane (125), its sulfoxide (126), and 3,4-dibromo-7-thiabicyclo[4.1.0]heptane (127) with DBU yielded benzene in 73, 70, and 38% yields, respectively (72JOC552).



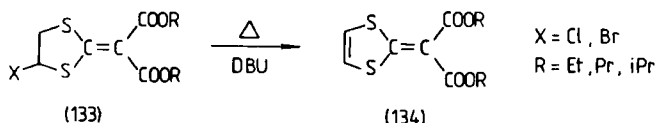
The reaction of  $\beta$ -lactones 128 with DBU in chloroform at 0–20°C gave arenes 129 in high yields, but  $\beta$ -lactone 130 afforded benzyl alcohol in low yield under similar conditions (76TL4435). In the latter case, the N-acylation



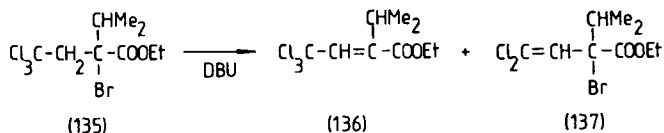
of DBU with lactone 130 was probably a side reaction. When the epoxide derivative 131 was treated with DBU, the acid-sensitive epoxylactone 132 was obtained in 91% yield.



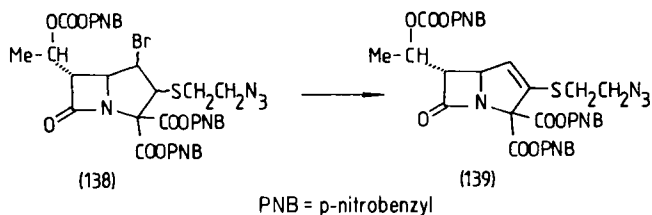
Dithiolyldenemalonates 134 were obtained in high yields from malonates 133 with DBU in refluxing toluene or xylene (79JAP26546; 79JAP(K)63084).



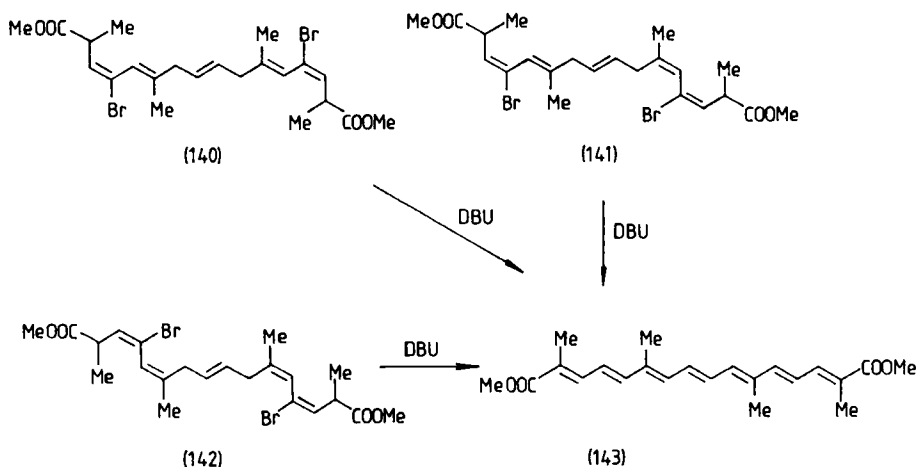
Treatment of ethyl 2-bromo-2-(2',2',2'-trichloroethyl)-3-methylbutyrate (**135**) with DBU gave a mixture of ethyl 2-isopropyl-3-trichloromethylacrylate (**136**) and ethyl 2-bromo-2-(2',2'-dichlorovinyl)-3-methylbutyrate (**137**) (79JAP(K)95528).



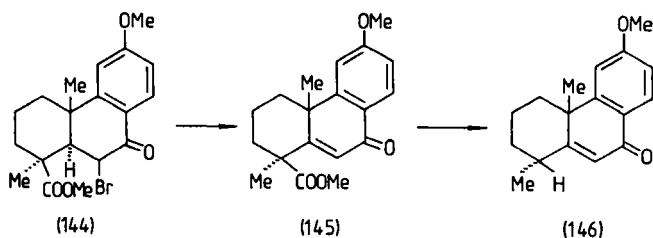
The reaction of pyrroloazetidinone **138** with DBU in dimethyl sulfoxide at ambient temperature under a nitrogen atmosphere gave the dehydrobrominated derivative **139** (77GEP2652676).



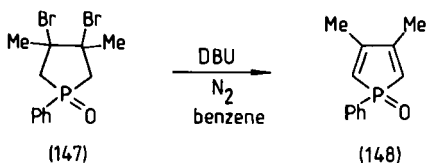
Crocetin dimethyl ester (**143**) was prepared from each of the isomeric dibromo esters (**140–142**) with DBU in different solvents at ambient temperature (77CB3582).



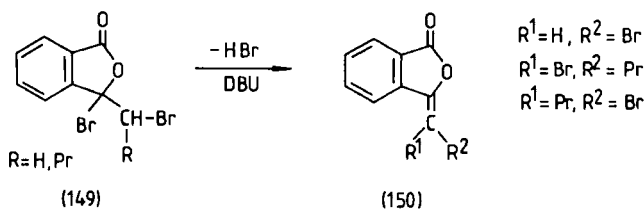
Treatment of the bromo ketone **144** with 2 mol equiv. of DBU in boiling *o*-xylene for 5 hr afforded a dehydrobrominated and decarbomethoxylated product (**146**) (73JOC1223). If the reaction was carried out for only 15 min, an elimination product (**145**) was obtained.



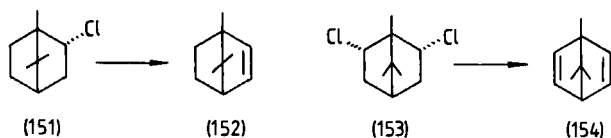
The reaction of 3,4-dibromo-3,4-dimethyl-1-phenylphospholane 1-oxide (**147**) with DBU in dry benzene under a nitrogen atmosphere gave 3,4-dimethyl-1-phenyl-phosphole 1-oxide (**148**) (75T53).



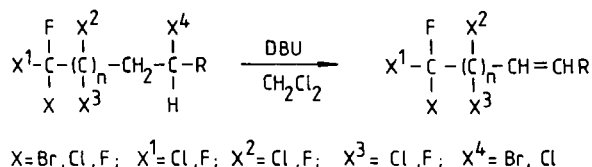
Treatment of 3-bromo-1(3*H*)-isobenzofuranones (**149**) with DBU afforded 3-(1-bromoalkylidene)-1-(3*H*)-isobenzofuranones (**150**) (85B1841).



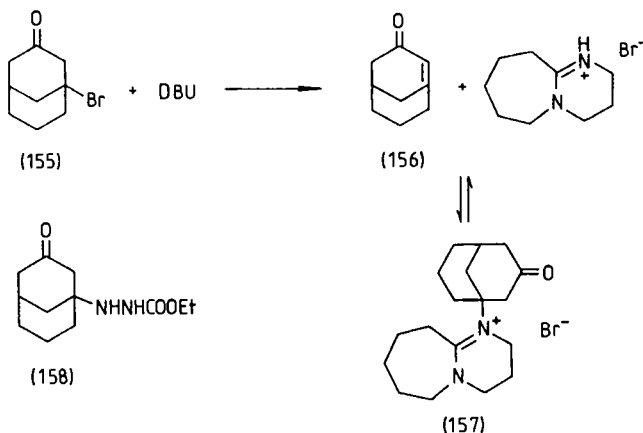
The treatment of bornyl chloride (**151**) and 2,6-dichlorocamphane (**153**) with DBU gave bornylene (**152**) and bornadiene (**154**) in low yields (82USP4289917). The application of alkoxide bases instead of DBU afforded better yields.



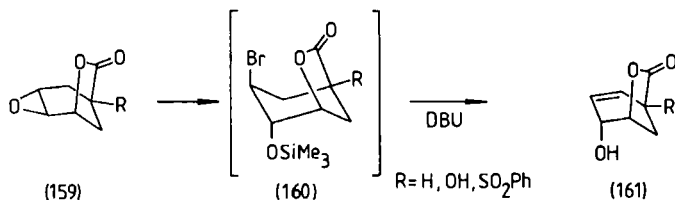
When treated with DBU in dichloromethane, fluorinated haloalkanes gave fluorinated alkenes (85MIP2519).



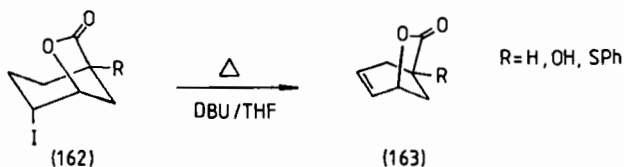
The formation of a mixture of unsaturated ketone **156**, DBU hydrobromide, and quaternary salt **157** was considered probable in the reaction of bromo ketone **155** and DBU in benzene. When the reaction between **155** and DBU was carried out in tetrahydrofuran in the presence of ethyl carbazate, the hydrazide **158** was isolated in 84% yield (79JOC3793).



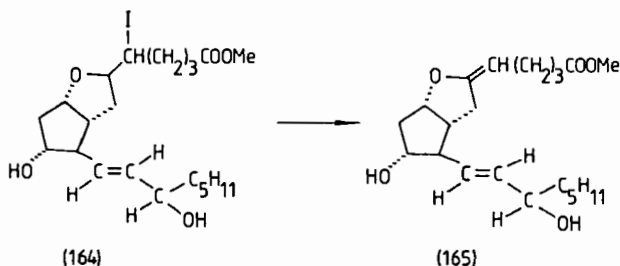
Epoxides **159** were converted to allylic alcohols **161** in high yields in acetonitrile in a one-pot procedure. The reaction involved triphenylphosphine-catalyzed epoxide opening with trimethylsilyl bromide, followed by elimination of the trimethylsilyl bromohydrin from **160** with DBU at reflux temperature (84JA7854).



The treatment of iodo lactones **162** with DBU in refluxing tetrahydrofuran afforded lactones **163** in high yields (84JA7854).



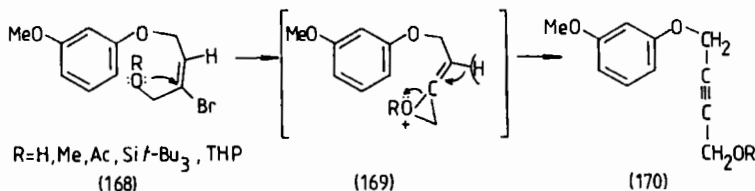
Dehydroiodination of prostanoid **164** with DBU in benzene gave **165** (78GEP2702553).



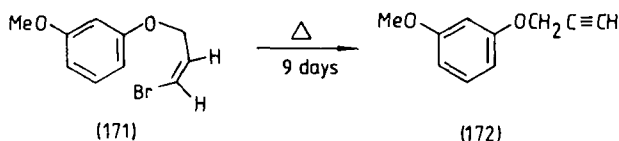
The unsaturated lactone **167** was obtained in 71% yield from iodo derivative **166** with DBU in refluxing benzene under a nitrogen atmosphere (75JOC1932).



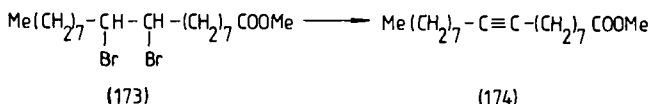
Schuda and Heimann reported that activated vinyl bromides **168** afforded acetylenes **170** on the reaction of DBU in refluxing benzene for 1–9 days, probably via allene oxide intermediates **169** (82JOC2484). (THP, Tetrahydropyranyl.)



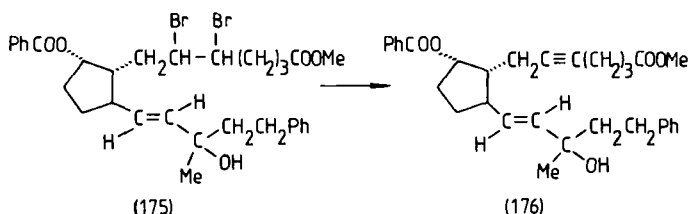
Under similar conditions, hydrogen bromide elimination occurred only from the (Z)-isomer of 1-bromo-3-[(3-methoxyphenyl)oxy]propene (**171**) to give acetylene **172** (82JOC2484).



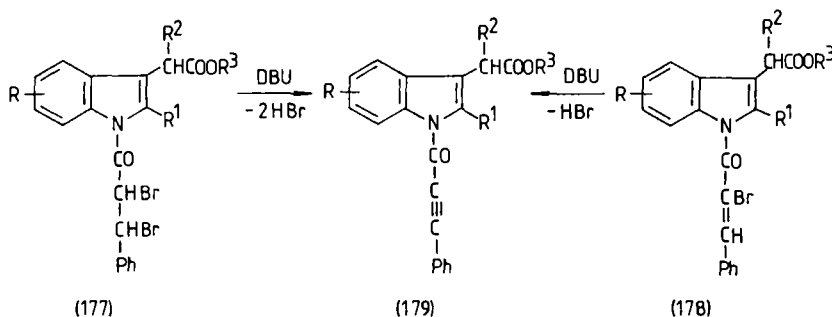
Methyl 9-octadecynoate (**174**) was obtained in 95% yield from the 9,10-dibromo ester **173** with DBU at 140°C in a nitrogen atmosphere (84JMC94).



Treatment of the vicinal dibromide **175** with DBU in tetrahydrofuran at 100°C under a nitrogen atmosphere for 7 hr yielded the acetylene derivative **176** (77USP4013695).



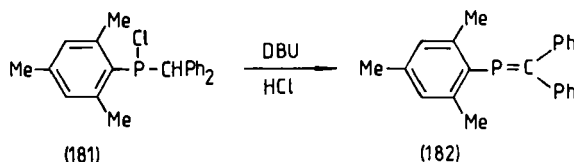
When the *N*-acylindoles **177** and **178** were heated in dimethyl sulfoxide at 80–90°C in the presence of DBU, acetylene derivatives **179** were produced (74JAP(K)72248).



Isocyanates were prepared in high yield from *N*-haloamides **180** with DBU in dimethylformamide (79JAP(K)128521).

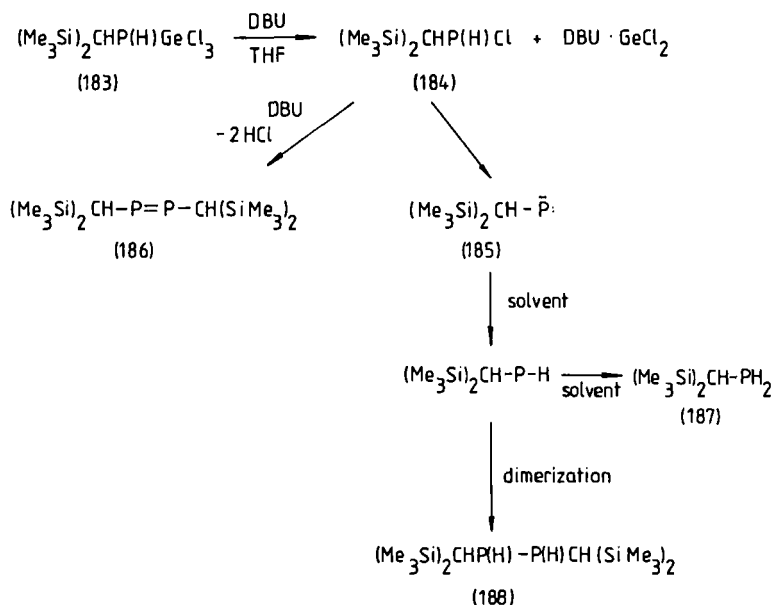


Dehydrochlorination of the phosphine derivative **181** with DBU in tetrahydrofuran at ambient temperature gave **182** in almost quantitative yield (78JA4886).



Treatment of trichlorogermylphosphine **183** with a twofold excess of DBU in tetrahydrofuran gave bis[bis(trimethylsilyl)methyl]diphosphene (**186**), bis(trimethylsilyl)methylphosphine (**187**), and diphosphine **188** in the proportions 55:25:20. The proposed reaction mechanism is depicted in Scheme 4. Compound **184** was probably first formed through the elimination of germanium dichloride, and then reacted further with an excess of DBU in two competitive reaction routes to give compounds **186**–**188**. Intermolecular dehydrochlorination of **184** afforded diphosphene **186**, while intramolecular dehydrochlorination of **184** resulted in **187** and **188** via the triplet phosphinidene intermediate **185** (84CC1621).

Dehydrochlorination of complexes of ruthenium(II), osmium(II), and

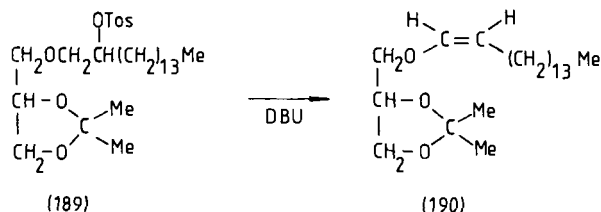


SCHEME 4

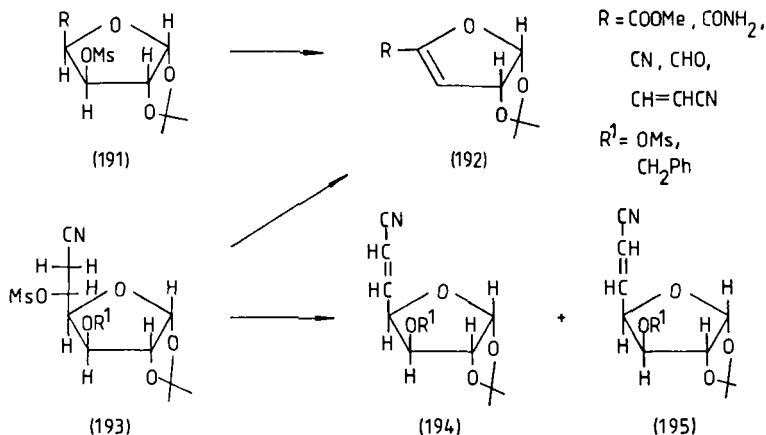
platinum(II) with DBU has been reported (81MI5). The complexes  $\text{MHCl}(\text{CO})(\text{PPh}_3)_3$  ( $\text{M} = \text{Ru}, \text{Os}$ ) were converted to  $\text{M}(\text{CO})_3(\text{PPh}_3)_2$  with DBU in toluene under 20–80 psi carbon monoxide. The complex  $\text{Pt}(\text{Ph}_2\text{C}_2)(\text{PPh}_3)_2$  was prepared in 82% yield from  $\text{PtHCl}(\text{PPh}_3)_2$  in refluxing methanol in the presence of DBU and diphenylacetylene.  $\text{Ru}(\text{CO})_2(\text{PPh}_3)_2$  was obtained from  $\text{RuHCl}(\text{CO})_2(\text{PPh}_3)_2$  and  $\text{Ru}(\text{CO})-(\text{CN}-p\text{-tolyl})(\text{PPh}_3)_2$  from  $\text{RuHCl}(\text{CO})(\text{CN}-p\text{-tolyl})(\text{PPh}_3)_2$  in refluxing methanol in the presence of DBU and triphenylphosphine.

Dehydrochlorination of  $\text{W}(\text{CO})_5[\text{PCl}(\text{mesityl})\text{CHPh}_2]$  with DBU gave *cis*- $\text{W}(\text{CO})_4[\text{P}(\text{mesityl})=\text{CPh}_2]$  in poor yield (81CC199).

Serebrennikova *et al.* reported that the detosylation of **189** with DBU afforded a pure *cis*-alkene ether (**190**) (69ZOR676).

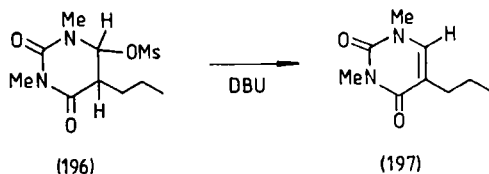


The demesylation of isopropylidene derivatives **191** and **193** with DBU in chloroform or diethyl ether at 0–20°C resulted in **192**, **194**, and **195** (72M218). The dimesyloxy derivative of **193** (R<sup>1</sup> = Ms) gave *cis*- and *trans*-**192** (R = —CH=CHCN).

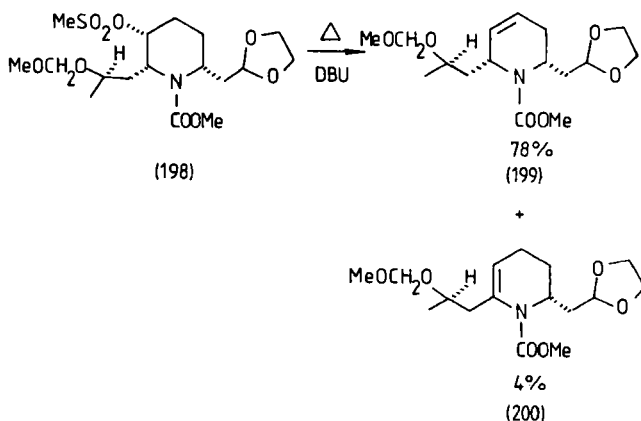


1,3-Dimethyl-5-propyluracil (**197**) was obtained in 48% yield when mesyloxy derivative **196** was treated with DBU in refluxing tetrahydrofuran (71JOC1251).

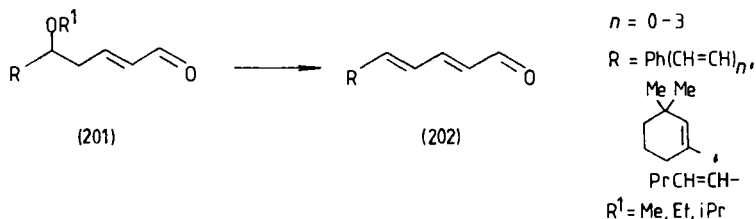




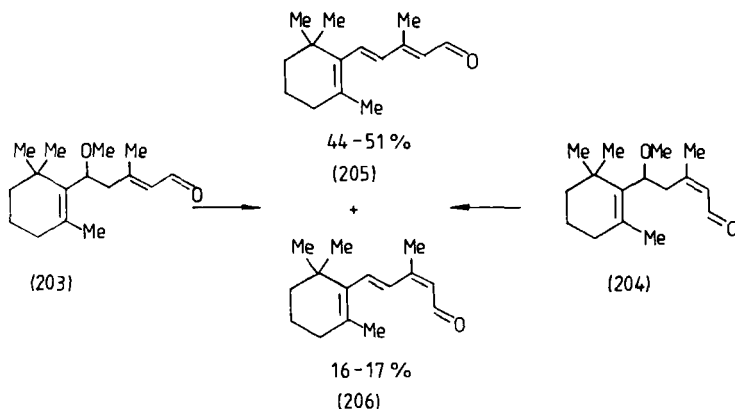
When the piperidine **198** was heated in DBU at about 70°C for 4 days, the required 1,2,3,6-tetrahydropyridine derivative **199** was accompanied by only 4% of by-product **200** (85H831).



$\delta$ -Alkoxy- $\alpha,\beta$ -unsaturated aldehydes **201** could be converted into the corresponding polyenals **202** in the presence of DBU and molecular sieves 3A or 4A in benzene, tetrahydrofuran, acetonitrile, or dichloromethane at



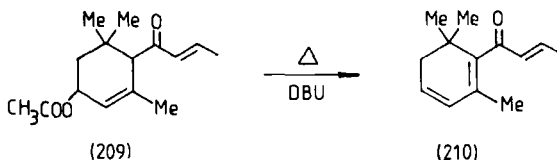
ambient temperature under an argon atmosphere (75CL1167). The application of pyridine, triethylamine, proton sponge, or 1,4-diazabicyclo[2.2.2]octane (DABCO) as base resulted in only poor yields. DBN gave similar results to those with DBU. Isomeric aldehydes **203** and **204** yielded the same ratio of products **205** and **206**.



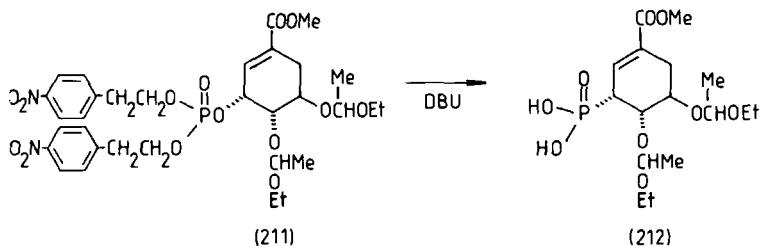
Conjugated dienenitriles **208** were prepared by dehydration of the corresponding hydroxy derivative (**207**) in the presence of a base (75GEP2456126; 76MI1). Among others DBU was applied.



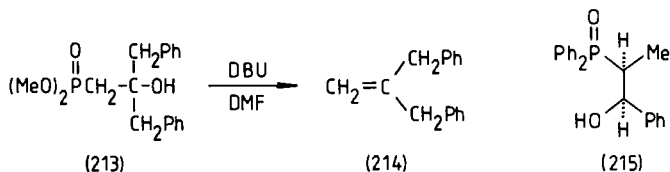
1,4-Elimination of acetic acid took place on treatment of acetoxycyclohexene derivative **209** with DBU at reflux temperature, to give  $\beta$ -damascenone (**210**) in 79% yield (79JOC3412).



Deprotection of the phosphate, without cleavage of the acetals, occurred in high yield on treatment of **211** with DBU in either chloroform or pyridine at ambient temperature (84JA7854).

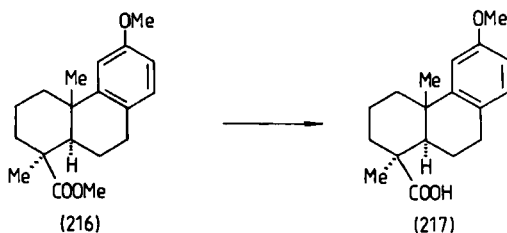


1,1-Dibenzylethylene (**214**) was prepared in 56% yield from dimethyl 2,2-dibenzyl-2-hydroxyethylphosphonate (**213**) by heating at 100–105°C in dimethylformamide in the presence of DBU for 14 hr (84CL1097).



Warren and co-workers reported that DBU did not influence the formation of olefin from *erythro*-(2-hydroxy-1-methyl-2-phenylethyl)diphenylphosphine oxide (**215**) in dimethylformamide (84JCS(P1)243).

Heating of methyl esters (e.g., **216**) with 10 mol equiv. of DBU in *o*-xylene resulted in O-methyl cleavage to give the corresponding acids (e.g., **217**) in excellent yields (73JOC1223). This method could also be applied to hindered esters (e.g., methyl mesitoate or methyl triisopropylacetate) and esters containing hydrolytically sensitive functional groups.



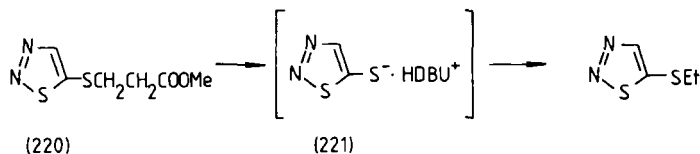
Ethyl 2,2-dimethyl-3-(2',2'-dichlorovinyl)cyclopropane-1-carboxylate (**219**) was obtained in 87% yield from the diethyl ester (**218**) by heating in xylene in the presence of DBU (78GEP2623848).



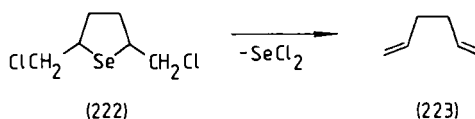
Different carboxylic acids were decarboxylated in the presence of DBU and copper(II) bromide at 25–360°C (81JAP(K)40616).

A reverse Michael reaction took place when 5-(methoxycarbonylthio)-1,2,3-thiadiazole (**220**) was heated in the presence of DBU in ethanol (79JHC1295). The salt formed (**221**) was alkylated *in situ* with ethyl iodide.

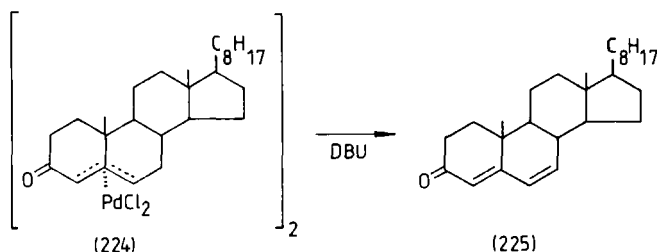
When 2,5-bis(chloromethyl)selenacyclopentane (**222**) was treated with



DBU in chloroform, 1,5-hexadiene (**223**) was formed in an exothermic reaction (69JOC4002).

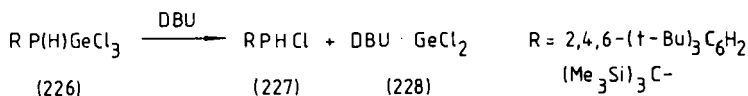


Treatment of di- $\mu$ -chlorobis[ $\alpha$ -4-6- $\eta$ -(3-oxocholestenyl)palladium(II)] (**224**) with DBU yielded dienone **225** in 11% yield in dichloromethane and in 35% yield in tetrahydrofuran (80AJC1537).

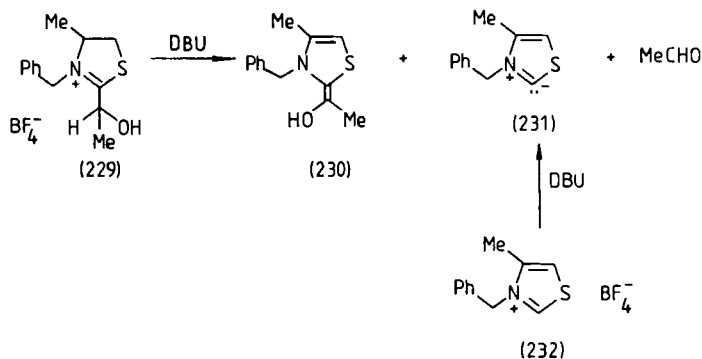


The reaction of trichlorogermylphosphines (**226**) with DBU gave chlorophosphine **227** and a DBU–germanium dichloride complex (**228**) (84CC1621).

Decarbonylation of alkyl formate was catalyzed by DBU to give alcohols and carbon monoxide (84EUP115387; 84USP4474744).



The reaction of thiazolium salt **229** with DBU in ethanol or tetrahydrofuran involved a competition yielding thiazoline **230**, ylide **231**, and acetaldehyde (79JA2752). Ylide **231** was also generated from the 3-benzyl-4-methylthiazolium salt **232** and DBU. Ylide **231** was trapped with different electrophiles. The reactions of **230** with sources of electrophilic sulfur mimic the pyruvate dehydrogenase-mediated production of enzyme-bound acetyl-dihydrolipoic acid.



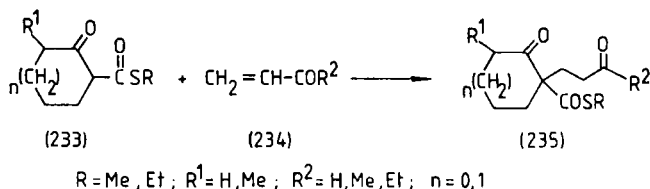
Whitney *et al.* used DBU or tetramethylguanidine as hindered and nonnucleophilic base for the removal of protected peptides from a 2-[4-(hydroxymethyl)phenylacetoxyl]propionyl resin (84T4237). The proposed reaction mechanism involved cleavage of the ester bond between the peptide and resin via a base-catalyzed elimination. This cleavage reaction was mild and rapid, and proceeded in good yield with a very simple work-up procedure.

Among other bases, DBU was applied unsuccessfully for the dehydrochlorination of chloro(dimesitylmethyl)mesitylphosphine and chlorobis(dimesitylmethyl)phosphine in tetrahydrofuran. When chloro(dimesitylmethyl)mesitylphosphine was heated with DBU in toluene, dimesitylmethane and an unidentified product resulted.

From dichloro(dimesitylmethyl)phosphine with DBU in tetrahydrofuran, the salt (dimesityleneCHPCIDBU<sup>+</sup>)Cl<sup>-</sup> was the probable product (84PS227).

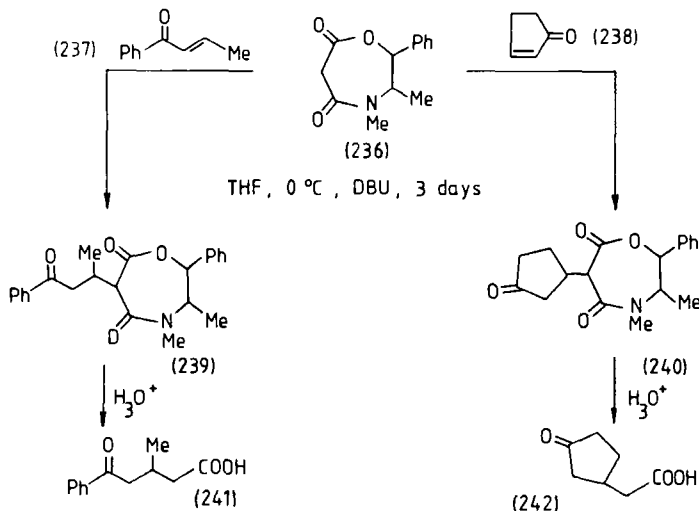
Some further reactions are to be found in Sections II,A,4,d and VI,B.

d. *Applications of DBU in Addition Reactions.*  $\beta$ -Ketothiol esters **233** underwent Michael reaction with conjugated enones **234** in the presence of DBU in 1,2-dimethoxyethane to give adducts **235** (81CJC1685). When DABCO was used instead of DBU, the yields were higher.

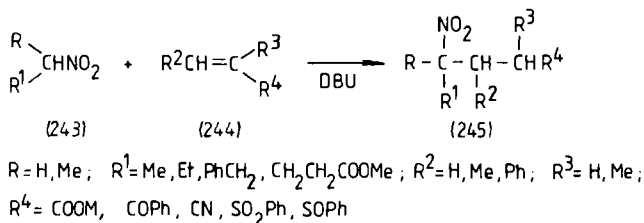


The Michael addition of (2*R*,3*S*)-3,4-dimethyl-5,7-dioxo-2-phenylperhydro-1,4-oxazepine (**236**) to 1-phenyl-2-buten-1-one (**237**) and 2-cyclopenten-1-one (**238**) in tetrahydrofuran at 0°C gave a mixture of diastereomeric

addition products **239** and **240**, which then were hydrolyzed and decarboxylated in refluxing acetic acid in the presence of 6 *N* sulfuric acid to give optically pure  $\delta$ -oxo carboxylic acids **241** and **242** in 55 and 96% yields, respectively (78CL461).



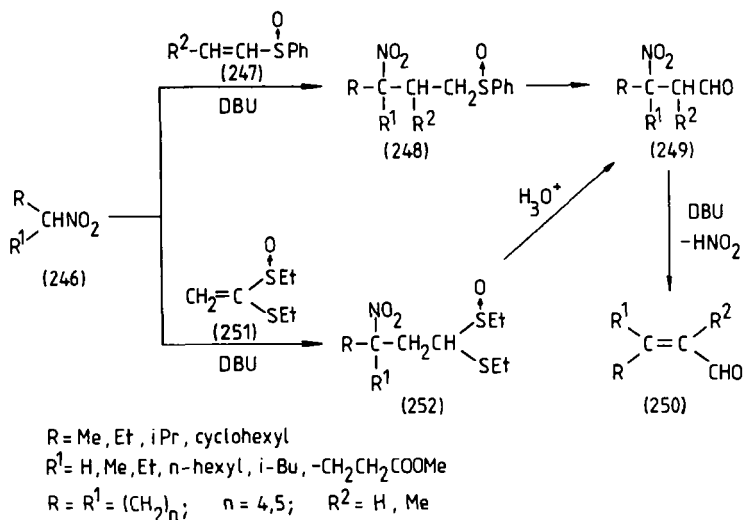
Nitro derivatives **245** were prepared in high yields by Michael addition of primary and secondary nitroalkanes **243** to  $\alpha,\beta$ -unsaturated carbonyl derivatives **244** in the presence of DBU in acetonitrile or dimethylformamide (83JAP(K)216144; 84S226; 85JOC3692). Triethylamine or tetramethylguanidine as base proved ineffective or less effective than DBU (84S226).



Tributyltin hydride can replace the nitro group by hydrogen without affecting other reducible groups, such as ester, cyano, keto, formyl, sulfinyl, and sulfonyl (85JOC3692).

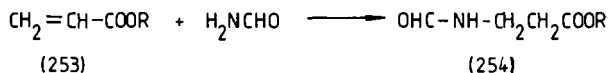
Michael addition of nitro compounds **246** to phenyl vinyl sulfoxides **247** in the presence of DBU in acetonitrile at room temperature gave adducts **248** in quantitative yields (82JOC5017). Other bases, such as triethylamine, potassium fluoride, and tetramethylguanidine, were not so effective as DBU.

Conversion of the adducts **248** afforded 3-nitroaldehydes **249**, which could be converted to olefins **250** with DBU in diethyl ether at ambient temperature.



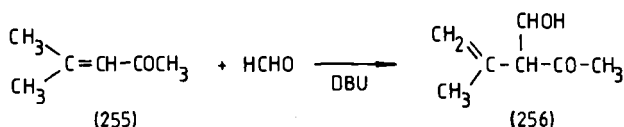
Similar reactions could also be carried out with ketene diethyl dithioacetal *S*-monooxide (**251**). The Michael addition of nitroalkanes **246** to **251** afforded the selective monoadducts **252**, but that to **247** ( $R^2 = H$ ) yielded a mixture of the mono- (**248**) and diadducts.

The reaction of acrylates **253** with formamide in the presence of DBU at  $80^\circ C$  afforded 3-(formylamino)propionates **254** in 50% yield (71GEP2004698).

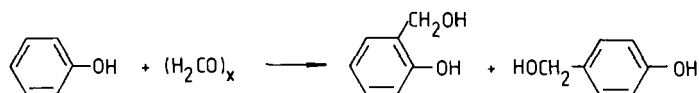


When a mixture of methanol and methyl acrylate was heated in the presence of DBU, methyl 3-methoxypropionate was obtained in 95% yield (85EUP136851). In the absence of DBU, the addition reaction did not occur.

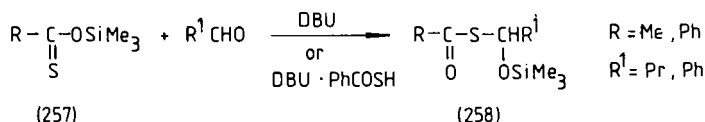
2-Methyl-3-(hydroxymethyl)pent-1-en-4-one (**256**) was prepared from 2-methylpent-2-en-4-one (**255**) with formaldehyde in the presence of DBU (77GEP2456413; 77GEP2456514).



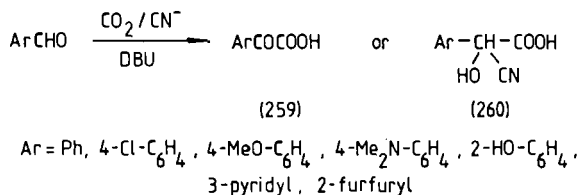
The reaction of phenol with paraformaldehyde in the presence of DBU led to a mixture of 2- and 4-hydroxybenzyl alcohols (81GEP2928554).



DBU or its salt with thiobenzoic acid catalyzed the reaction between (thioacyloxy)silanes **257** and aldehydes at room temperature to give addition products **258** in quantitative yields (81BCJ790).



Aromatic aldehydes were carboxylated by treatment with carbon dioxide and potassium cyanide in the presence of DBU under pressure in dimethylformamide at ambient temperature to give  $\alpha$ -oxo carboxylic acids **259** or their cyanohydrin derivatives **260** (77JAP(K)27745).

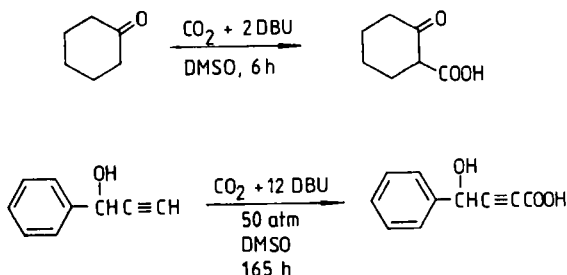


Carboxylic acids could be prepared from compounds containing an active hydrogen atom with dry carbon dioxide in the presence of 2–12 mol equiv. of DBU at ambient temperature in dimethylformamide or dimethyl sulfoxide, or without solvent (74CL427; 77JAP(K)202). The yields of the carboxylic acids increased with the pressure of carbon dioxide (77JAP(K)202).

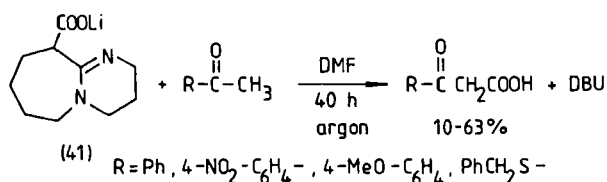
Iwatani *et al.* carried out a kinetic investigation of the carboxylation of cyclohexanone with carbon dioxide in dimethyl sulfoxide in the presence of DBU (78MI4). The effects of the initial concentration of DBU and cyclohexanone, the pressure of carbon dioxide, and the temperature on the carboxylation were studied. The kinetic data suggested that the carboxylation involved the initial formation of a complex of DBU and carbon dioxide, which transferred carbon dioxide to the substrate in the rate-determining step.

Matsumura *et al.* recently reported that the lithium carboxylato derivative **41**, prepared from DBU and carbon dioxide in the presence of butyllithium,



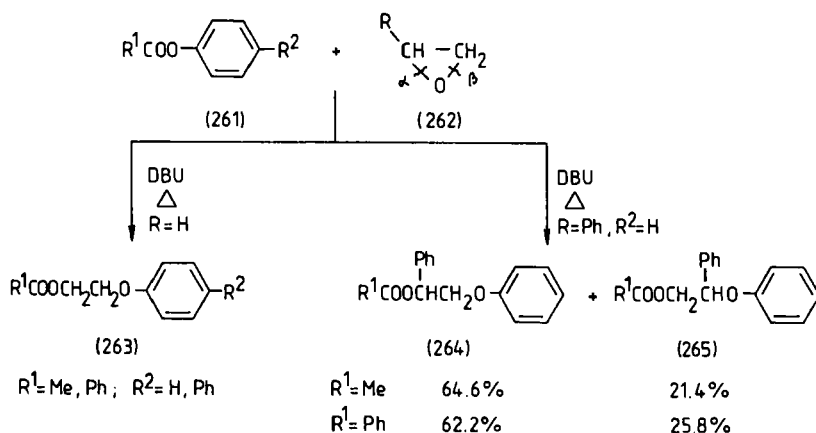


could be used for carboxylation of the active methyl group at room temperature in dimethylformamide (83CL317). Compound **41** is isolable and stable for several hours under argon at ambient temperature.



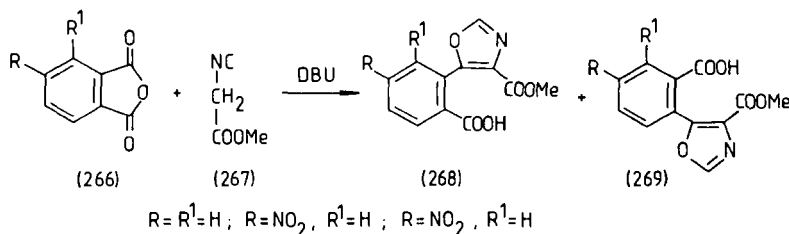
2-Hydroxyethyl esters were prepared from carboxylic acids and ethylene oxide in the presence of DBU (73JAP(K)37003).

Oxiranes **262** reacted with aryl esters **261** in the presence of DBU to give the esters **263–265** in high yields (79BCJ1488). Cleavage of the C—O bond in **262** denoted by  $\beta$  resulted in the formation of esters **264**, whereas cleavage of the C—O bond denoted by  $\alpha$  gave rise to **265**.

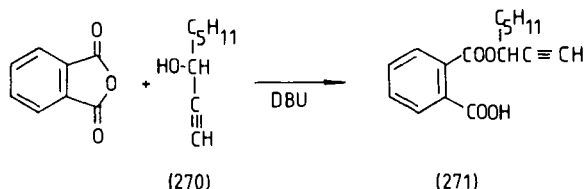


The reaction of aliphatic carboxylate esters or ethers with carbon monoxide in the presence of nickel or a nickel derivative, iodine or an iodine compound, and an organic trivalent Group VA element compound and DBU under pressure gave carboxylic acid anhydrides (79GEP2844371).

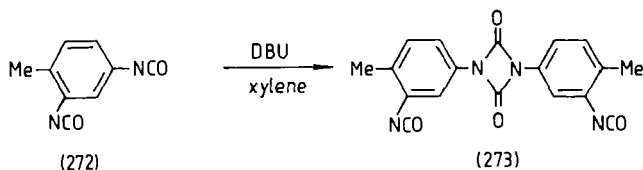
The reaction of phthalic anhydrides **266** with methyl isocyanoacetate (**267**) in tetrahydrofuran in the presence of DBU gave a mixture of oxazole-4-carboxylates **268** and **269** (79CPB1373; 79JAP(K)70285). Subsequently, products **268** and **269** were transformed into 1-oxoisoquinoline-3-carboxylates in two steps.



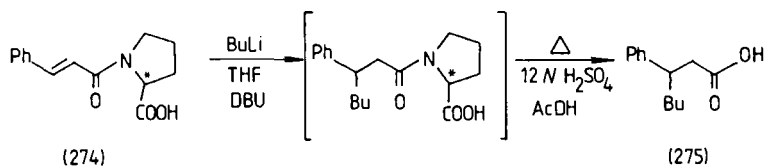
The treatment of phthalic anhydride with 1-octyn-3-ol (**270**) in the presence of a few drops of DBU yielded the half-ester **271** (75JAP(K)106934).



2,4-Diisocyanatotoluene (**272**) was treated with DBU in xylene to give 1,3-bis(4'-methyl-3'-isocyanatophenyl)uretidinedione (**273**) in 93.3% yield (71JAP(K)37503).



Soai *et al.* investigated the effects of amines on the diastereoselectivity of the conjugate addition of butyllithium to the  $\alpha,\beta$ -unsaturated amide **274**, derived from the  $\alpha$ -amino acid of *S*-proline. When DBU was applied as base, (–)-(*R*)-3-phenylheptanoic acid (**275**) was obtained in 55% e.e. (83SC27).



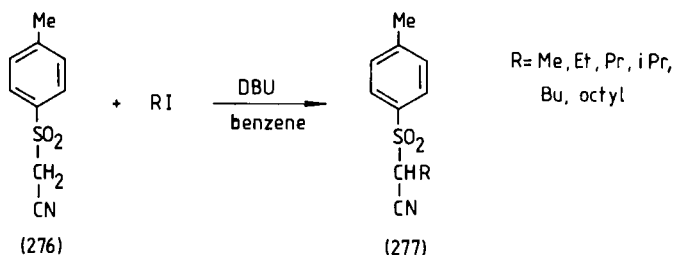
Alkyl formates were prepared in insertion reactions of alcohols with carbon monoxide, catalyzed by a mixture of DBU and an epoxide (84EUP104875).

The mechanism of formation of methyl formate from methanol and carbon monoxide in the presence of DBU has been investigated (77NKK457). In the resulting equilibrium, the rate of formation of methyl formate was found to be first order with respect to the carbon monoxide pressure and to the concentrations of methanol and DBU.

*e. Applications of DBU in Substitution and Condensation Reactions.* Active methylene groups can be alkylated in the presence of DBU. Depending on the reaction conditions, mono- or dialkylated products are obtained.

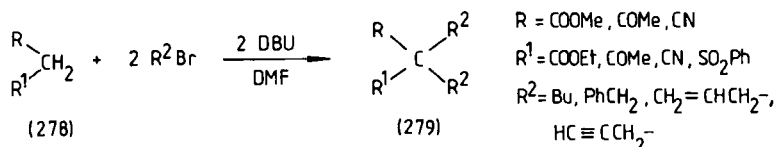
Ono *et al.* studied the monoalkylation of methyl cyanoacetate and acetylacetone with alkyl bromides and iodides in the presence of 1.02 mol equiv. of DBU in benzene at room temperature (77CL871). The products were analyzed by gas chromatography (GC). Dialkylation occurred only in 1–8% yield. For acetylacetone, O-alkylation was also observed, in about 3–10% yield. The amount of dialkylated product was higher if the alkylation was carried out in acetonitrile or if some other bases were applied (sodium hydroxide in dimethylformamide, methanolic sodium methylate, or tetrabutylammonium hydroxide in chloroform).

Monoalkylated products **277** were obtained in 41–75% yields when tosylacetone (276) was reacted with 2 mol equiv. of alkyl iodide in the presence of 1.0 mol equiv. of DBU in benzene at ambient temperature (77S690). With ethyl iodide the amount of diethylated product was only 0.5%.

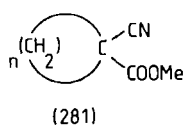
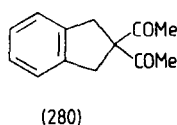


The conventional methods (sodium hydride in dimethylformamide or triethylbenzylammonium chloride under phase-transfer conditions) resulted in the formation of considerable amounts (13–48%) of the diethylated product.

Reaction of compounds **278** with 2.2 mol equiv. of alkyl bromide in the presence of 2.2 mol equiv. of DBU in dimethylformamide at 75–80°C gave dialkylated derivatives **279** in 75–91% yields (73GEP2206778; 76LA348).

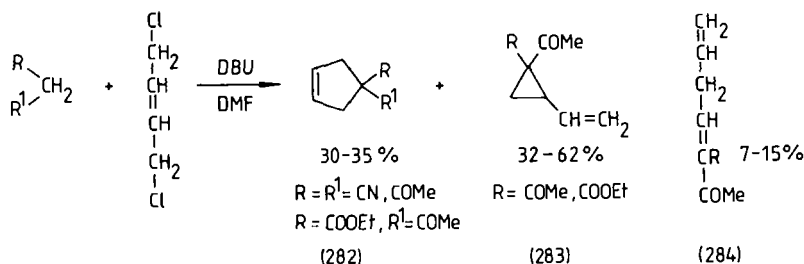


Application of 1,2-bis(bromomethyl)benzene or  $\alpha,\omega$ -dibromoalkanes gave cycloalkyl derivatives **280** and **281** in low or moderate yields (76LA348).

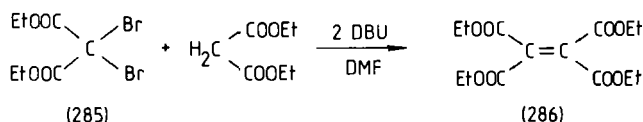


n = 2	5 %
n = 3	10 %
n = 4	61 %
n = 5	63 %

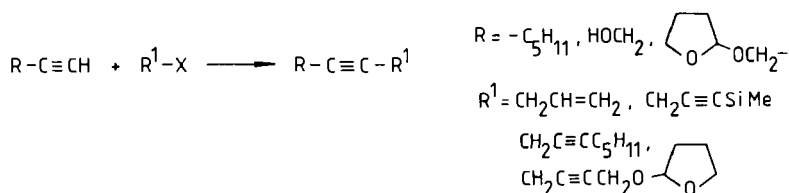
Whereas the reaction of malononitrile with 1,4-dichloro-2-butene led to 4,4-dicyanocyclopentene (**282**,  $R = R^1 = \text{CN}$ ), from acetylacetone and ethyl acetoacetate an isomeric mixture of compounds **282–284** was obtained (76LA348).



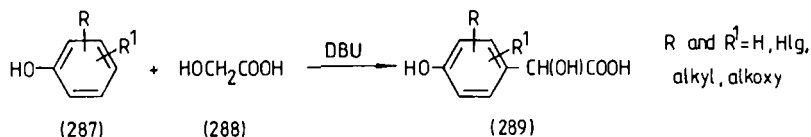
Treatment of diethyl dibromomalonate (**285**) with diethyl malonate in the presence of 2 mol equiv. of DBU in dimethylformamide afforded tetraethyl ethylenetetracarboxylate (**286**) in 65% yield (76LA348).



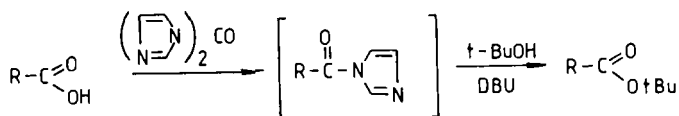
A complex of DBU and copper(I) halide (chloride or iodide) was used for the alkylation of terminal acetylene groups in an inert solvent and in the presence of a small amount of hydroxylamine hydrochloride under an argon atmosphere (75FPR2243172; 75GEP2344985; 78LA658).



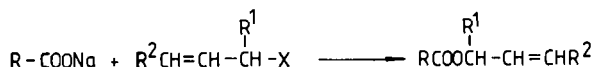
The reaction of phenols **287** with glycolic acid (**288**) in the presence of DBU gave hydroxymandelic acids **289** in good yields (81JAP(K)68641).



*tert*-Butyl carboxylates can be prepared in high yields directly from acids in a one-pot procedure in the presence of *N,N'*-dicarbonyldiimidazole and DBU (82S833).

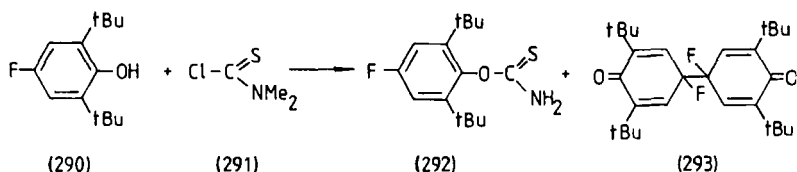


With alkyl bromides or iodides in the presence of DBU in benzene, acids, including sterically hindered acids (e.g., 2,4,6-trimethylbenzoic acid), thermally labile acids (e.g., malonic acid), and *N*-protected amino acids were readily esterified in good yields (78BCJ2401). In the case of malonic acid and cyanoacetic acid, C-alkylation was not observed, and hydrogen bromide elimination did not take place when secondary bromides or phenethyl bromide were applied. Carboxylic acids bearing an amino or hydroxy group were esterified without protection of these groups. *N*-Protected amino acids could be esterified without racemization. The principle of this esterification with DBU in benzene resembles that of the ion-pair extractive alkylation or the method using crown ether. In the first step, a hydrogenbond develops between DBU and the carboxyl proton; the hydrogen-bonded complex, which is a strong nucleophile but a weak base, then attacks the carbon atom rather than the hydrogen atom of alkylating agents.



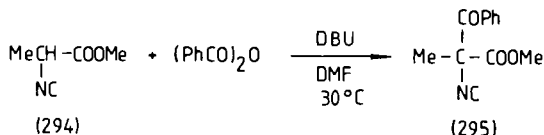
Allyl esters were prepared in 36–67% yield from alkali metal carboxylates with allyl halides in the presence of DBU (75JAP(K)108210). Triethylamine was a less effective catalyst than DBU.

The reaction of 4-fluoro-2,6-di-*tert*-butylphenol (290) with *N,N*-dimethylthiocarbamoyl chloride (291) in the presence of DBU in dimethylformamide

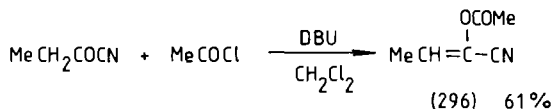


under a nitrogen atmosphere afforded **292** and the bis derivative **293** in 20 and 10% yields, respectively (72CB1087).

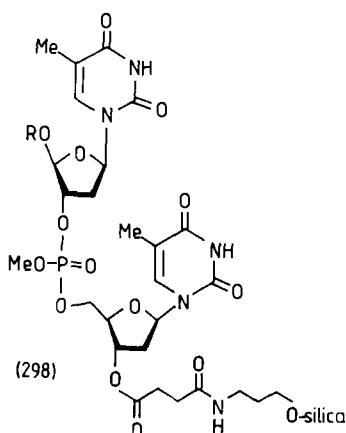
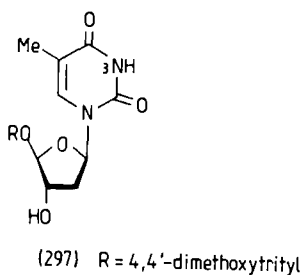
Treatment of methyl  $\alpha$ -isocyanopropionate (**294**) with benzoic anhydride in dimethylformamide in the presence of DBU furnished the  $\alpha$ -benzoyl derivative **295** in 65% yield (73JOC3571).



Acetylation of 2-oxobutyronitrile with acetyl chloride in the presence of 1 mol equiv. of DBU in dichloromethane gave 1-cyanopropenyl acetate (**296**) (80BCJ3337).



5'-(Dimethoxytrityl)thymidine (**297**) and silica-bound oligonucleotides containing the thymidine moiety (e.g., **298**) were alkylated at N-3 of the thymidine with triethyl proosphate in the presence of DBU in pyridine at ambient temperature (85MI3). Application of DBU resulted in a significantly faster alkylation than that with triethylamine.

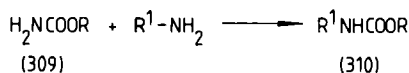


The reaction of 4-chloronitrobenzenes **299** with anilines **300** in the presence of DBU, copper(I) oxide, and potassium carbonate in refluxing xylene gave 4-nitrodiphenylamines **301** (83GEP3137041).



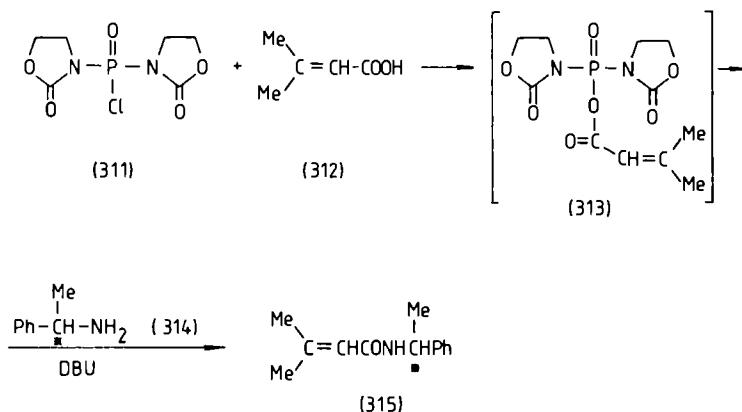
Substituted ureas were prepared from amines and urea in the presence of a catalyst mixture containing DBU (81GEP2943480; 82MIP2481699; 85USP4501915).

Alkyl carbamates **309** reacted with primary amines in the presence of DBU to give N-substituted carbamates **310** (82MIP2479209; 82USP4336402).

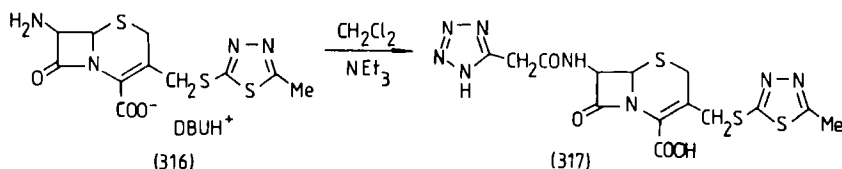


Cellulose was acylated with acetic anhydride in the presence of lithium chloride and DBU to give cellulose diacetate (83GEP3227267).

Carboxamides were prepared from acids and amines in the presence of *N,N'*-bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride (**311**) and a tertiary base (84S413). In the first step, an ester (e.g., **313**) was formed, which then reacted with amines to give carboxamides. In this way, optically active amide **315** was prepared in 74% yield from 3,3-dimethylacrylic acid (**312**) and optically active  $\alpha$ -methylbenzylamine (**314**) in the presence of **311** and DBU in dimethylacetamide.



The DBU salt of 7-amino-3-(5-methyl-1,3,4-thiadiazol-2-yl-thiomethyl)-3-cephen-4-carboxylic acid (**316**) in dichloromethane was acylated with the mixed anhydride of tetrazolylacetic acid and pivalic acid or with tetrazolylacetic anhydride to afford **317** (82EUP53077; 82MIP497076).

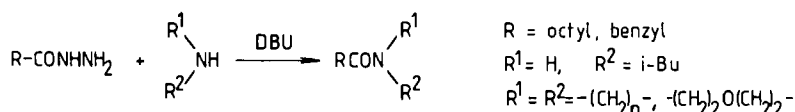




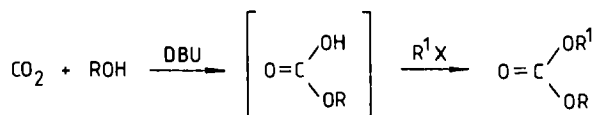
DBU was found to be an excellent catalyst in the preparation of acid chlorides from carboxylic acids or anhydrides at 70–105°C (70GEP1931074; 74JOC1134). Thus, lauroyl chloride was obtained in 96.0% yield from lauric acid (74JOC1134).

The conversion of carbohydrazides to carboxamides in tetrahydrofuran with copper(II) chloride catalyst required only 1 mol equiv. of amine in the presence of DBU. However, if DBU was not present, 5 mol equiv. of amine was necessary (80T1311).

The formate salt of DBU was obtained when carbon dioxide and hydrogen were reacted in the presence of a salt of a Group VIII metal (e.g.,  $\text{RuCl}_3$ ) and DBU in alcohol (84EUP95321).

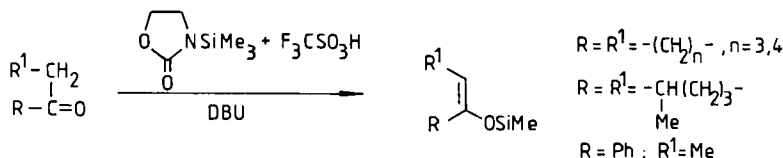


Dialkyl carbonates were prepared by reacting alcohols or water with carbon dioxide in the presence of DBU, followed by alkylation (82JAP(K)58645).



Formamidines were prepared from carbon monoxide, methanol, and amines in the presence of DBU and a mixture of a Group VA Lewis base and alkene oxide (84EUP107441).

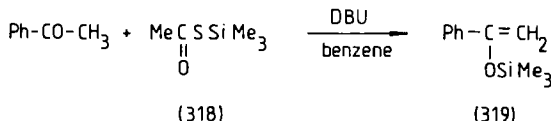
Ketones could be silylated with trimethylsilyl triflate, generated *in situ* from *N*-trimethylsilyl-2-oxazolidinone and triflic acid in the presence of DBU, to give the enol silyl ether in excellent yields (84CJC336).



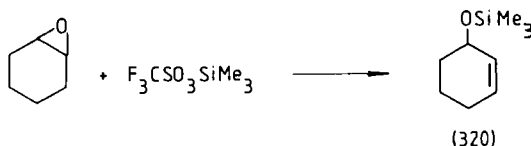
DBU was also used in the *tert*-butyldimethylsilylation of alcohols, phenols, mercaptans, thiophenols, carboxylic acids, amines, and ketones with *tert*-butyldimethylchlorosilene in dichloromethane, benzene, or acetonitrile at room temperature or at 80°C (85TL475). Good chemoselectivity was observed in the case of alcohol. The formation of primary silyl ethers was the quickest,

while that of tertiary silyl ethers was the most sluggish. Base-sensitive structures, such as the  $\beta$ -lactam ring, were unaffected under the silylation conditions.

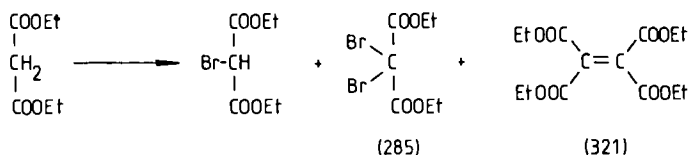
The reaction of acetophenone with thioacetyloxysilene (**318**) in the presence of an equimolar amount of DBU in benzene at ambient temperature gave the O-silylated enolate **319** in 38% yield (81BCJ790).



Treatment of 1,2-epoxycyclohexane with trimethylsilyl trifluoromethanesulfonate in the presence of DBU in benzene at ambient temperature afforded 3-trimethylsilyloxycyclohexene (**320**) in 87% yield (81JAP(K)43289).

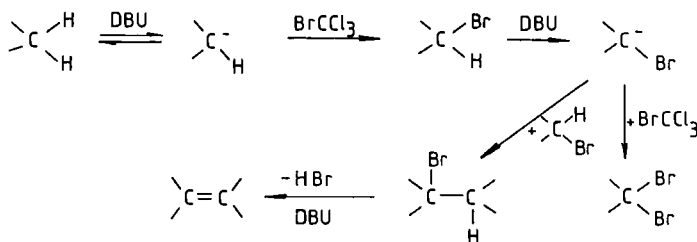


Compounds containing active hydrogen atoms ( $\text{p}K_a = 11\text{--}25$ ) could be brominated when DBU was added dropwise into a mixture of substrate (phenylacetylene, diethyl butylmalonate, indene, or fluorene) and  $\text{BrCCl}_3$  in benzene (78CL73). Compounds with lower acidity ( $\text{p}K_a \geq 29$ ) exhibited no reaction. With more acidic derivatives (diethyl malonate and benzyl cyanide), oxidative dimerization also occurred. Oxidative dimerization also took place when  $\text{BrCCl}_3$  was added dropwise into a solution of active methylene compound and DBU in benzene. The ratio of the reaction products depended on the ratio of DBU and  $\text{BrCCl}_3$ .



DBU + CBrCl <sub>3</sub>				
mol	mol			
3	1.7	45 %	0 %	38 %
3	6	0 %	30 %	50 %

The proposed reaction mechanism for dimerization is depicted in Scheme 5 (78CL73).

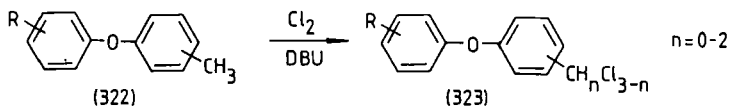


SCHEME 5

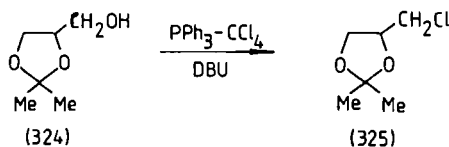
Treatment of diethyl malonate with DBU- $\text{CCl}_4$  reagent at room temperature gave diethyl dichloromalonate and the dimeric product **321** in 48 and 26% yields, respectively (78MI1).  $\text{CBr}_4$  and  $\text{BrCCl}_3$  were also used in place of  $\text{CCl}_4$ .

Under similar conditions, benzyl cyanide gave *trans*-dicyanostilbene in 70% yield, whereas fluorene afforded fluorenone in 70% yield (78MI1).

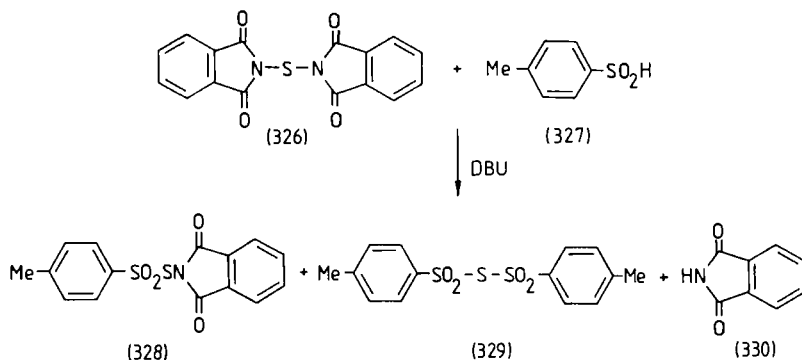
Phenoxytoluenes **322** were chlorinated with gaseous chlorine in the presence of DBU to give derivatives mono- di-, or trichlorinated in the side chain (**323**) (81JAP(K)89237; 84USP4399075).



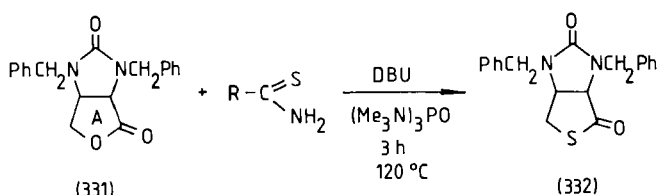
Chlorination of (*S*)-2,2-dimethyl-1,3-dioxolane-4-methanol (**324**) with triphenylphosphine and carbon tetrachloride in the presence of a base gave 4-chloromethyl-2,2-dimethyl-1,3-dioxolane (**325**) (84MI4). The best stereoselectivity was achieved on the application of DBU.



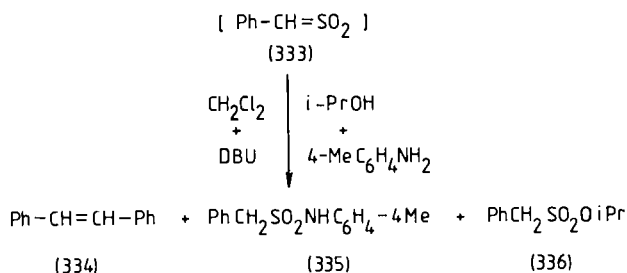
*N,N'*-Dithiodipthalimide (**326**) reacted with 1 mol equiv. of *p*-methylbenzenesulfinic acid (**327**) in refluxing dichloromethane in the presence of a catalytic amount of DBU to give compounds **328** and **329** in 59 and 1% yields, respectively (80BCJ3678). If the reaction was carried out with 2 mol equiv. of *p*-methylbenzenesulfinic acid, phthalimide **330** and compound **329** were isolated in 92 and 77% yields, respectively.



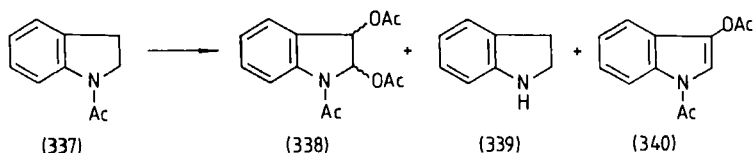
Treatment of bicyclic compound **331** with a thioamide in the presence of DBU resulted in oxygen  $\rightarrow$  sulfur exchange in ring A to give **332** (79JAP(K)112288).



King and Kang investigated the competitive trapping of phenylsulfene (**333**) by isopropanol and 4-methylaniline in the presence of different bases (75CC52). With DBU, stilbene (**334**), amide **335**, and ester **336** were obtained in 27, 38, and 30% yields, respectively.

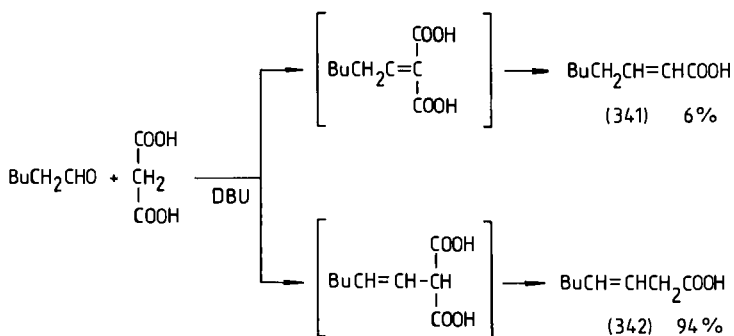


Electrochemical acetoxylation of *N*-acetylindoline (**337**) in acetic acid in the presence of DBU using platinum foil electrodes gave the 2,3-diacetoxy derivative **338** in 77% yield, together with two minor products—**339** and **340**—in 3 and 2% yields, respectively (78JOC2882).

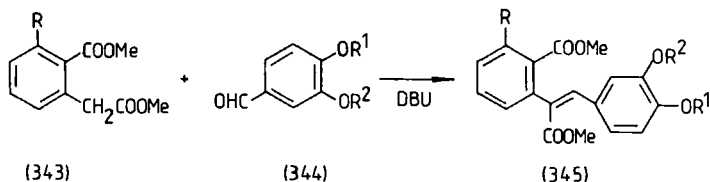


DBU was used in the electropreparation of 1-acyloxy-3,4-dialkoxybenzenes from 1,2-dialkoxybenzenes in a nitrile, amide, or ketone (80JAP(K)79883).

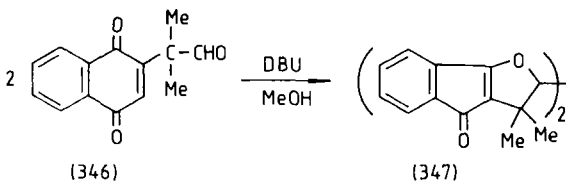
The Knoevenagel condensation of hexanal and malonic acid to give 2- and 3-octenoic acids (**341** and **342**) was investigated in the presence of different bases (83H1541). The amines used could be classified into two groups. Bases containing a basic center with no steric hindrance (e.g., pyridine) afforded predominantly 2-octenoic acid (**341**), whereas bases containing a sterically crowded basic center (e.g., DBU or triethylamine) yielded mainly 3-octenoic acid (**342**). When DBU was applied, the ratio of **341** and **342** was 6:94.



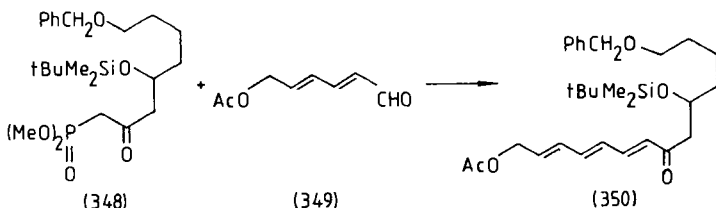
The condensation of homophthalates **343** with benzaldehydes **344** in the presence of 1 mol equiv. of DBU afforded stilbene derivatives **345** in 57–80% yields (730PP81; 75SC387). 4-Hydroxybenzaldehydes failed to react under similar conditions (75SC387).



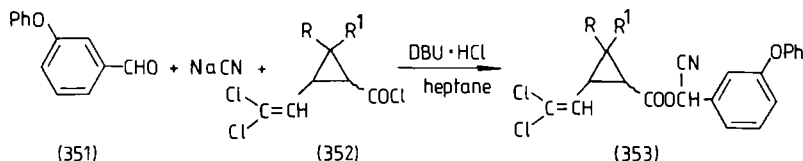
On the action of DBU in methanol at  $-10^\circ\text{C}$ , two molecules of naphthoquinonylmethylpropionaldehyde (**346**) fused to form the indenofuranone **347** in 32% yield (72LA44).



Olefinations by Horner–Wadsworth–Emmons reactions that involve a base-sensitive substrate or reagent can be carried out from aldehydes and phosphates in acetonitrile in the presence of DBU and lithium chloride. The reaction yields olefins in 85–100% yields with a high (*E*):(*Z*) ratio (20:1) after a reaction time of 5 min–1 hr (84TL2183). The lithium cation forms a tight complex with the carbanion derived from the phosphonates, enhancing the acidity of the latter. When diisopropylethylamine was applied instead of DBU, a longer reaction period (from 7 hr to 3 days) was required. The condensation reaction of phosphonate **348**, which is prone to undergo elimination of a molecule of alcohol under basic conditions, with unsaturated aldehyde **349** gave unsaturated ketone **350** in 70% yield in the presence of DBU and lithium chloride at room temperature.



The reaction of 3-phenoxybenzaldehyde (**351**), sodium cyanide, and acyl halides **352** in the presence of DBU hydrochloride in aqueous heptane resulted in  $\alpha$ -cyanoesters **353** in 99% yield (80MIP6222; 81USP4254052; 82USP4323685).

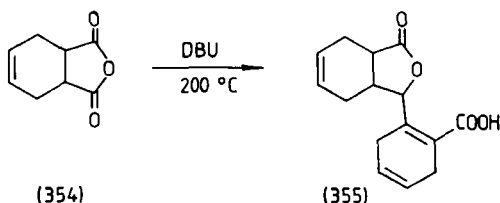


Phthalocyanines could be prepared in high yields by reacting phthalonitriles with alcohols in the presence of DBU (80CL1277; 83JAP(K)23854; 83JAP(K)105962). If a metal salt was also present in the reaction mixture, metallophthalocyanines were obtained (83CL313; 83JAP(K)127763).

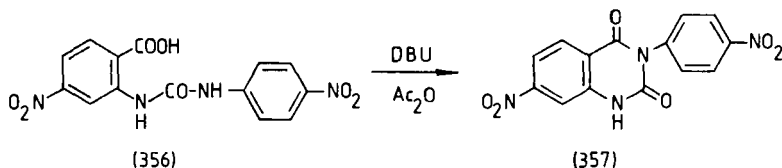
The reaction between lutetium (III) acetate and 1,2-dicyanobenzene in refluxing 1-hexanol in the presence of DBU gave the lutetium diphthalocyanine

( $\text{LuPc}_2 \cdot \text{CH}_2\text{Cl}_2$ ) and the monophthalocyanine derivative [ $\text{LuPc}(\text{OAc})(\text{H}_2\text{O})_2 \cdot \text{H}_2\text{O} \cdot 2\text{CH}_2\text{Cl}_2$ ] after chromatography on a column of silica gel with  $\text{CH}_3\text{OH}-\text{CH}_2\text{Cl}_2$  eluent (85IC3162).

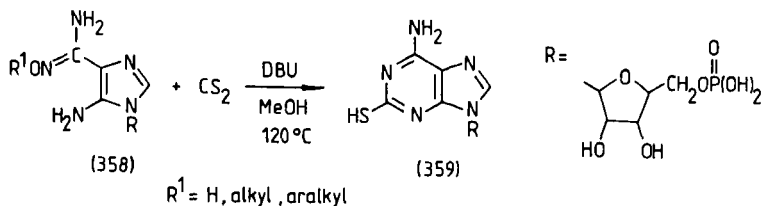
Tetrahydrophthalic anhydride (**354**) was refluxed in the presence of DBU to give a decarboxylated condensation product (**355**) (84JAP(K)67280).



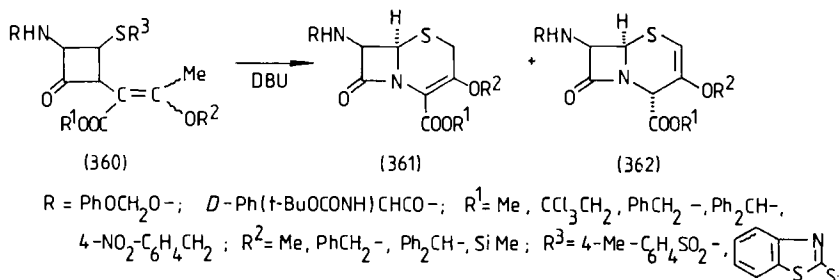
f. *Applications of DBU in Cyclization and Cyclocondensation Reactions.* With acetic anhydride in the presence of DBU in cyclohexanone at 95–110°C, 2-[*N'*-(*p*-nitrophenyl)ureido]-4-nitrobenzoic acid (**356**) was cyclized to 3-(*p*-nitrophenyl)-7-nitroquinazoline-2,4-dione (**357**) in 84.5% yield (75GEP2315302).



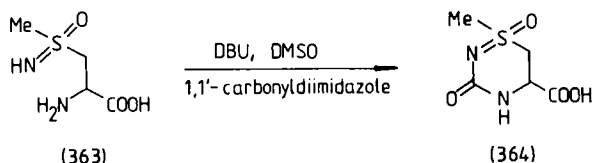
The reaction of 5-aminoimidazole-4-carboxamidoximes **358** with carbon disulfide in methanol in the presence of DBU yielded 2-thioadenosine derivatives **359** (77JAP(K)80896).



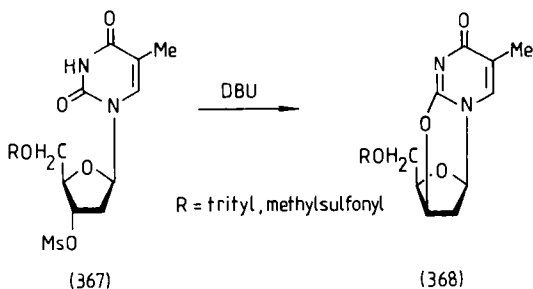
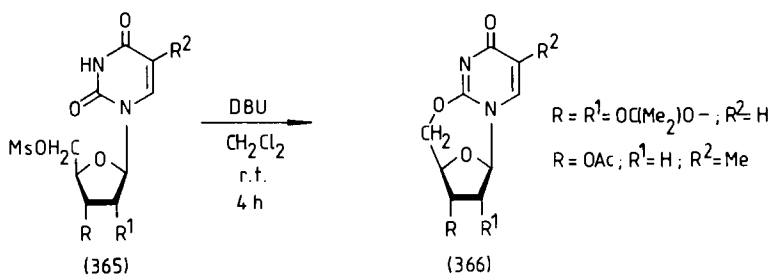
Cyclization of an isomeric mixture of 2-(2-oxoazetidin-1-yl)crotonates and isocrotonates (**360**) in the presence of DBU in an inert solvent at 0–25°C gave a mixture of 2- and 3-cephem-4-carboxylates (**361** and **362**) (76GEP2506330).



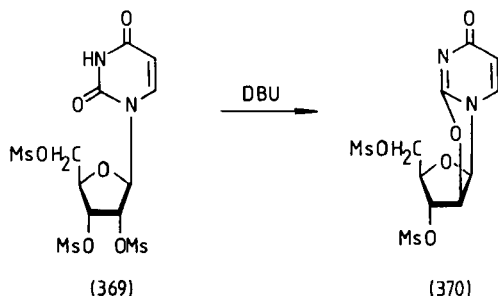
3-Oxo-1-methyl-3,4,5,6-tetrahydro-1*H*-1,2,4-thiadiazine-5-carboxylate 1-oxide (364) was obtained in 87% yield from (*S*)-methylcysteine sulfoximine (363) with 1,1'-carbonyldiimidazole in the presence of DBU in dimethyl sulfoxide (84JMC228).



Secrist reported the facile synthesis of uracil and thymine anhydronucleosides **366**, **368**, and **370** in good yields under mild conditions in the presence



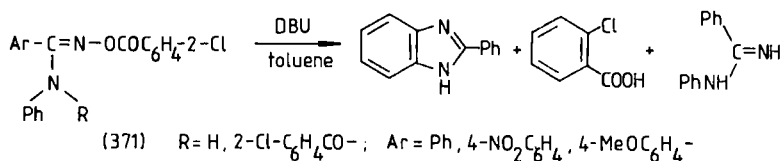




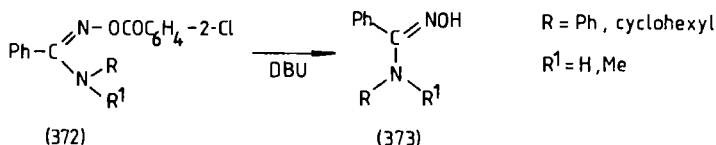
of DBU (75MI3). Nucleosides **365**, **367**, and **369** were stirred at ambient temperature in dichloromethane with slightly more than 1 mol equiv. of DBU to give the anhydronucleosides in 69–97% yields. 1,5-Diazabicyclo[4.3.0]non-5-ene proved to be a less effective reagent than DBU.

The reaction of amidoximes with DBU gave a nitrene intermediate, which reacted further in routes depending on the reaction conditions to give different products (75BSF2677).

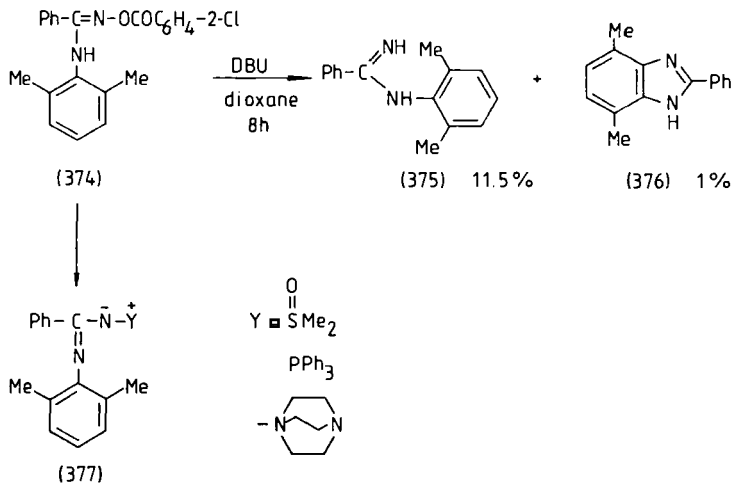
Treatment of amidoximes **371** with DBU in toluene at 80°C for 1 hr gave 2-phenylbenzimidazole and 2-chlorobenzoic acid in high yields. In the case of formamidine **371** (R = H; Ar = H), traces of *N*-phenylbenzamidine were also isolated.



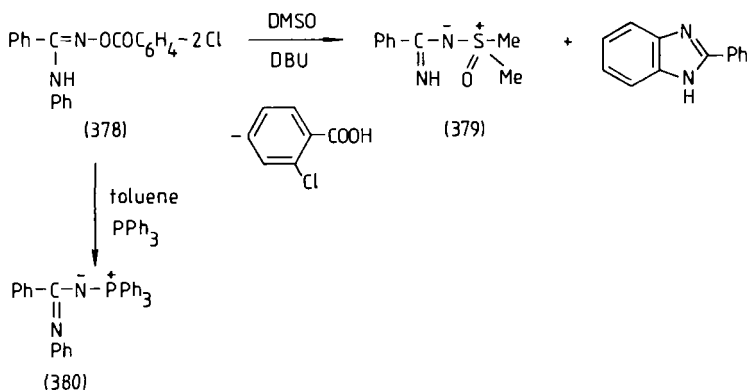
When benzamidoximes **372** were heated in toluene in the presence of DBU, amidoximes **373** and 2-chlorobenzoic acid were obtained.



Treatment of compounds **374** with DBU in refluxing dioxane yielded benzamidine **375** and traces of benzimidazole **376**. However, this reaction led to the respective ylides **377** in 39–94% yield if it was carried out in dimethyl sulfoxide or toluene in the presence of triphenylphosphine or DABCO.



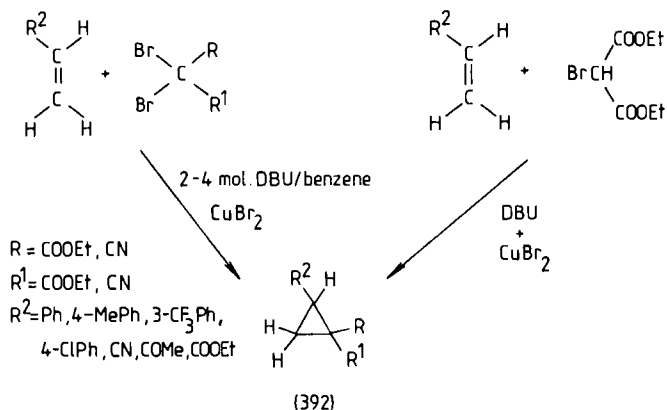
Benzamidoxime **378** gave a mixture of ylide **379** and 2-phenylbenzimidazole with DBU in dimethyl sulfoxide at 80°C, whereas in toluene in the presence of triphenylphosphine, ylide **380** was obtained (75BSF2677).



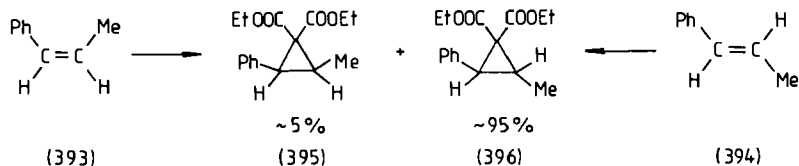
A mixture of methyl isocyanatoacetate and DBU was treated dropwise with aldehydes in tetrahydrofuran at 40–50°C to give 3-substituted pyrrole-2,4-dicarboxylates **386** in 43–71% yields (74JOC1980; 76ABC2271; 76JAP(K)128963). The proposed reaction mechanism is depicted in Scheme 6 (76ABC2271). In the first step, addition product **381** was probably formed, which lost 1 mol of water to give condensation product **382**. Michael addition of a second mole of methyl isocyanatoacetate to the 2-isocyanatoacrylate **382** then gave **383**, which subsequently cyclized to **384**. In the following steps, elimination of hydrogen isocyanide yielded **385**, and proton migration resulted in the formation of 3-substituted pyrrole-2,4-dicarboxylate (**386**).



Electrophilic cyclopropanes **392**, which are useful intermediates in organic syntheses, can be prepared by the cyclopropanation of olefins with diethyl dibromomalonate and its derivatives (81MI4). The reaction is carried out in the presence of 1 mol equiv. of copper(II) bromide and 2–4 mol equiv. of DBU. Alternatively, the reaction can be effected with diethyl bromomalonate (83BCJ2687) in the presence of a catalytic amount of copper(II) bromide and a slight excess of DBU in benzene at ambient temperature. When some other base (e.g., triethylamine, DABCO, pyridine, or sodium hydride) was applied instead of DBU, the yield was lower or no reaction occurred. The use of other copper salts led to a decrease in the yield. When cyclopropanation was carried out in dimethyl sulfoxide, dimethylformamide, or acetonitrile, the yield of product **392** was again lower.

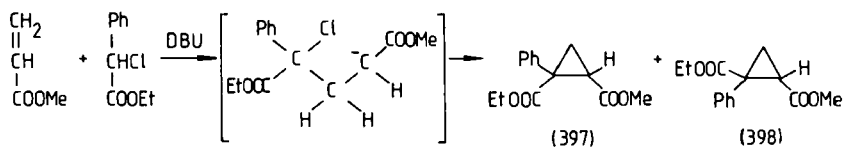


The cyclopropanation of (*E*)- and (*Z*)- $\beta$ -methylstyrene (**393** and **394**) led to essentially the same ratio of (*E*) and (*Z*) cyclopropane derivatives **395** and **396**, indicating that the reactions proceeded stereospecifically (81MI4; 83BCJ2687). As electron-deficient olefins such as acrylate and acrylonitrile reacted even in the absence of copper(II) bromide, while the reaction of styrenes required the copper salt as catalyst, it was concluded that the reaction mechanism may vary, depending on the nature of the olefin.



The base-catalyzed cyclocondensation of methyl acrylate with ethyl

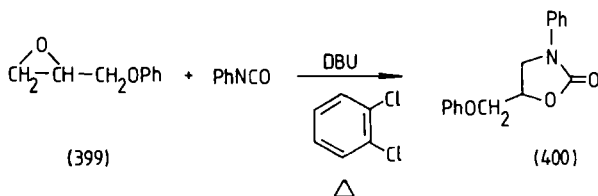
phenylchloroacetate led to the formation of *cis*- and *trans*-cyclopropane-1,2-dicarboxylates **397** and **398** (82ABC1027). When DBU was applied as base, the *cis*-*trans* ratio depended only slightly on the nature of the solvent.



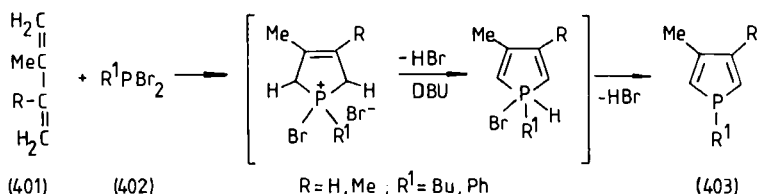
Aziridine was prepared by heating 1,2-dichloroethane and ammonia at 80°C in the presence of DBU (74JAP(K)14456).

The condensation of diethyl succinate in the presence of ethanolic sodium ethylate and DBU in xylene at 80–100°C gave diethyl 2,5-dihydroxy-1,4-cyclohexadiene-1,4-dicarboxylate (77JAP(K)5739).

When phenyl glycidyl ether (**399**) and phenyl isocyanate were heated in the presence of DBU in *o*-dichlorobenzene, 3-phenyl-5-phenoxyethyl-2-oxazolinone (**400**) resulted in 93% yield (75JAP(K)117771). In the presence of DBU in dimethylformamide, bisphenol A diglycidyl ether and bis(4-isocyanatophenyl)methane gave polyoxazolidone in 96% yield.



Butadienes **401** reacted with phosphines **402** in the presence of DBU in a mixture of benzene and dichloromethane at ambient temperature to afford phosphorus derivatives **403** in 12–52% yields (70BSF4433).



## 5. Applications of DBU in the Synthesis of Macromolecules, and Other Applications of DBU

DBU and its salts and quaternary salts have been applied as catalysts or components of catalysts for the manufacture of polyurethanes (69FRP1542058; 70FRP1564939; 70JAP(K)40553; 70JAP(K)40554;

71JAP25017; 71JAP(K)10188; 72JAP25138; 74USP3769244; 77GEP2710901; 79USP4124573; 81JAP(K)50918; 83JAP(K)215415; 85JAP(K)84319, polyurethane foams (70GEP1950262; 80JAP(K)73765; 81JAP(K)98222; 82MI1, 83GEP3202327; 84MI1; 84USP4431753), cellular urethane polymers (73JAP55231), and polyurethane coatings (81GEP2940333; 85EUP132057; 85GEP3435469; 85MI2); for the preparation of polyureas (79GEP2722514; 81MI3), anticlouding coatings (80JAP(K)90563), polyoxymethylenes (79JAP(K)94549), aromatic polyesters (84JAP(K)89323; 84JAP(K)159821; 85JAP(K)53529; 85JAP(K)53530; 85JAP(K)53532; 85JAP(K)112821), polyarylene polyethers (78JAP(K)73298), polymers (75GEP2410066; 75JAP(K)70452; 75MI4; 76BRP1404927; 77GEP2642137; 80JAP(K)86818), fluoropolymers (85BEP900047), electrically conductive resin pastes (85JAP(K)1222), and fluorine elastomer compositions (73GEP2255170; 73JAP(K)55231); for the molding of polyisocyanurate heat-resistant resins (84JAP(K)221321), PVC pastes (78JAP(K)11950), resins (74JAP(K)80198; 74JAP(K)106584; 83JAP(K)132018), epichlorohydrin copolymer rubber (81JAPK4628), cellulose carboxylic acid esters (83GEP3227267), and for diene rubbers (84USP4424323); for the copolymerization of oxetane with carbon dioxide (84MI6); and for the production of silicone antireflective coatings on plastic lenses (83JAP(K)42001).

DBU and its salts have been used as heat stabilizers for polyoxymethylenes (79JAP(K)16595; 79JAP(K)16596; 79JAP(K)17994), antioxidants for epichlorohydrin-ethylene oxide rubber (78JAP(K)69254), and as cross-linking catalysts and agents for urethane polymer coatings (71JAP(K)10549), polyurethane adhesives (85EUP124753; 85USP4515933), siloxane coatings (78GEP2803942; 82JAP(K)38863; 82JAP(K)38864; 85JAP(K)92351), epoxyresin sealing compounds (84JAP(K)182583), polyvinyl formal coatings (83JAP(K)96657), epoxy resins (72FRP2094671; 72GEP2034389; 72JAP1115; 72USP3622540; 76JAP(K)17299; 76JAP(K)26999; 77GEP2034389; 79JAP(K)29399; 79JAP(K)127458; 80JAP(K)5929; 80JAP(K)98262; 80MIP1804; 82JAP(K)23620; 83JAP(K)84820; 83JAP(K)118817; 83JAP(K)145724; 83JAP(K)145725; 83JAP(K)154715; 84JAP(K)8721; 84JAP(K)75923; 84JAP(K)136321), fluoropolymer coatings (85EUP131419; 85USP4487878; 85USP4490501; 85USP4495248), phenolic resins (77JAP(K)117992; 77JAP(K)117993; 83JAP(K)69242; 83JAP(K)118817; 84JAP(K)75923), phenol novolak-silicone compounds (84JAP(K)172541), PVC (80JAP(K)98565), PVC plastisols (80JAP(K)137146), insulating resin pastes (85JAP(K)4521), novolak epoxy potting (82JAP(K)210647; 83JAP(K)57427; 85JAP(K)47019), acrylic polymers (78JAP(K)25655), epichlorohydrin rubber (76JAP(K)110487), and nitrile-based rubber (83JAP(K)118817). They have been used in the preparation of waste tire rubber sheets (83JAP(K)65642) and self-adhesive

insulated wire (84JAP(K)159640); as photographic fog inhibitors for photo-development emulsions (81JAP(K)144438); and as dissociation catalysts in the preparation of coatings (83JAP(K)65764; 83JAP(K)65765).

DBU and its salts and quaternary salts have been applied as vulcanization accelerators, vulcanizing catalysts, and agents for polymers (76JAP(K)8352; 76JAP(K)38328), epichlorohydrin rubbers (75JAP(K)107047; 75JAP(K)107048; 75JAP(K)112451; 75JAP(K)113561; 75JAP(K)149742; 75JAP(K)149743; 75JAP(K)151956; 75JAP(K)151957; 75JAP(K)155557; 75JAP(K)156560; 76JAP(K)26959; 76MI3; 77JAP(K)19754; 77JAP(K)32947; 77JAP(K)89163; 77JAP(K)155660; 77USP4032479; 78JAP(K)96057; 78JAP(K)101050; 79JAP(K)157158; 80EUP4087; 80USP4196255; 83JAP(K)103555; 83JAP(K)162335), halogen-containing polymers (84JAP(K)227945; 84JAP(K)227947), epichlorohydrin rubber-nitrile rubber blends (77JAP(K)32948), epichlorohydrin rubber-fluorocarbon rubber blends (79GEP2856526), acrylic rubber (77JAP(K)32948; 78JAP(K)112950; 78JAP(K)115769; 79JAP(K)83953), polyethylene rubbers (76JAP(K)20249), fluoro rubbers (74JAP(K)87722; 74JAP(K)87740; 74JAP(K)87741; 74JAP(K)89740; 75GEP2418717; 75JAP(K)46753; 78JAP(K)94361; 80JAP(K)45734; 81JAP(K)90836; 81JAP(K)147840; 81JAP(K)161448; 82JAP(K)153; 82JAP(K)164142; 82JAP(K)200437; 83JAP(K)103555; 83JAP(K)162335; 83JAP(K)162336; 85JAP(K)18535), PVC rubbers (76JAP(K)50346), fluoro-elastomer compositions (76GEP2532288; 84JAP(K)217749; 85EUP140207), moisture-curable silicone rubbers (85GEP3411716), liquid butyl rubber (78JAP(K)88043), and nitrile rubber (85JAP(K)18535).

DBU and its salts have been patented and used as dehydrohalogenation agents for fluoropolymers (83JAP(K)219202), fluororubbers (78MI3), and poly(vinyl halide) in the preparation of polarizing films (83JAP(K)21929), and as dissociation catalysts for blocked isocyanates (83JAP(K)65764).

DBU and its salts have been employed as curing agents for transparent novolak epoxy resin potting compounds (84JAP(K)43825), desensitizers for copying papers (74GEP2328312; 77GEP2553083; 82MIP2476100), inhibitors in the isomerization of 3,4-dichloro-1-butene (73GEP2145877), reclaiming agents for tire wastes (79JAP(K)1391; 79JAP(K)17985; 80MI1; 80MI2), stabilizers for silkworm growth promoter agents (80JAP(K)85504; 80MIP1418), photographic stabilizers, (77BRP1448575), catalysts for the isomerization of maleic anhydride-decatriene reaction products to give liquefying products useful for curing epoxy resins (82USP4332733), mold release agents for polyurethane foams (76GEP2431968), liquid crystal compositions (77GEP2646485), cross-linking agents for hydrophilic epoxy resin adhesives for wet wood (76JAP(K)41406), and vulcanizable fluoroelastomer compositions (82JAP(K)209950).

DBU and its salts have been applied in chlorosulfonated polyethylene coating compositions (85USP4513060), electroconductive paste compositions (85JAP(K)44533), epoxy resin potting (85JAP(K)4527; 85JAP(K)112817), powder potting (85JAP(K)86175; 85JAP(K)88080), molding (85JAP(K)69131) compositions, room temperature-vulcanizable organopolysiloxane compositions (85USP4517337), potting compositions (85JAP(K)64483), and rust-inhibiting paint compositions (85JAP(K)28465).

DBU and its salts have been utilized in the manufacture of polyisocyanate binders (85GEP3328662), metal phthalocyanine polymers (85JAP(K)47027), and resin-sealed light-emitting apparatus (85JAP(K)70781).

DBU has been incorporated into the plastic coverings of electrical cables to prevent damage by ants (82JAP(K)212703).

The influence of reaction temperature increase on the catalytic effects of DBU (83MI3), and the specific catalysis of DBU for polyurethane formation (83MI2), have been studied.

The influence of DBU mono(2-ethylhexanoate) catalysis on the processability and physical properties of high-resiliency polyurethane foams has been reported (81MI2).

DBU and its salts have been applied in the preparation of sulfoethyl quaternary ammonium salts (84JAP(K)205371); in the formation of polarizing films (81JAP(K)72401; 81JAP(K)106212); in the polymerization of formaldehyde (74JAP(K)62590; 79GEP2816339; 79JAP(K)73894; 79JAP(K)73895; 79NEP8247); in hardener compositions for asphalt (75JAP(K)119899); in the preparation of polyelectrolytes (78JAP(K)37793); in the manufacture of aromatic polyamide polyhydrazide fibers (78JAP(K)69252); in different corrosion inhibitor materials (70GEP1939789; 71JAP(K)2169; 71JAP(K)2170; 71JAP(K)2171); in lubricating oils (74JAP24333); in the potting of semiconductor devices (84JAP(K)141250); in steel-treating agents (78JAP(K)129133); in catalysts for the oxidative coupling of 2,6-dialkylphenols (69BRP1134613); in photographic stabilizer agents (74JAP(K)11321; 75GEP2343531); in silver dispersions for filter and antihalation layers (77GEP2559191); in photodevelopable photographic emulsions for improved images (80BEP878090); in surfactant compositions (82JAP(K)133199); in adhesives (85JAP(K)28480); in urethane adhesives (82JAP(K)117577; 83JAP(K)21470); in acrylic resin-based pressure-sensitive adhesive (83JAP(K)34878); in the removal of resins from wood (82JAP(K)66904); and in the preparation of nonsilver light film (83JAP(K)60737), photosensitive resin layers (84JAP(K)72438), polyisocyanates (81MI1), and thermosetting resin blend moldings (84JAP(K)189158).

Isocyanate-epoxy reactions have been investigated bulk and in solution in the presence of DBU and other bases (85MI1).

The catalytic activities of main Group II-IV metal complexes of DBU have



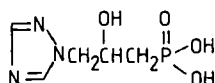
been studied with respect to the ring-opening polymerization of ethylene carbonate (84MI2). The synthesis, structure, and properties of polyene films made by the dehydrochlorination of PVC films with DBU have been reported (84MI8).

## 6. Miscellaneous

DBU is an effective cocatalyst for the homogeneous water gas shift reaction catalyzed by  $\text{Ru}_3(\text{CO})_{12}$  or by  $\text{Os}_3(\text{CO})_{12}$  under basic conditions (83CL1837; 85NKK503).

7-Aminocephemcarboxylates were solubilized in organic solvents with DBU, and were then acylated (82EUP53077; 82MIP497076).

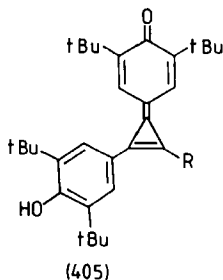
DBU salts of the herbicide 3-triazolyl-2-hydroxypropylphosphonic acid (**404**) have been prepared (83EUP78613).



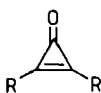
(404)

DBU has been used to study the kinetics and isotope effects in the proton-transfer reactions between DBU and 4-nitrophenylnitromethane (77CC695; 78JCS(F1)2065) in toluene; between DBU and 1-(4-nitrophenyl)-1-nitroethane (82CJC1692; 84MI5) in acetonitrile and toluene; and between DBU and 2,4,6-trinitrotoluene (81BCJ2598; 82JPC3418; 83JA7676; 84BCJ366; 84JCS(P2)655) in acetonitrile, benzonitrile, dichloromethane, and 1,2-dichloroethane. In these proton-transfer reactions the isotope effects on the activation parameters in different solvents indicated that tunneling of the proton through the potential energy barrier made a significant contribution to the reaction rate.

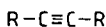
Compounds **405** and **406** in tetrahydrofuran underwent deprotonation directly to dianions on the action of DBU (84JOC965). Deprotonation of



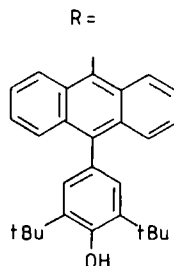
(405)



(406)



(407)



R =

**407** proceeded very slowly with either DBU or sodium hydroxide in tetrahydrofuran.

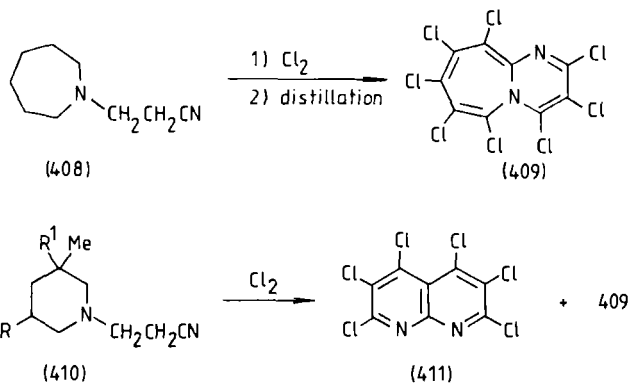
DBU proved to be a mild inhibitor of indoleamine *N*-methyltransferase obtained from rabbit and human lung ( $IC_{50}$  8.0 mmol liter<sup>-1</sup> and 25.7 mmol liter<sup>-1</sup>, respectively) in *in vitro* experiments (79JMC237).

DBU can be regained from its hydrochloride salt in 93% yield by treatment with sodium ethoxide in ethanol (75JAP(K)59369).

## B. OTHER PYRIMIDO[1,2-*a*]AZEPINES

### 1. Synthesis

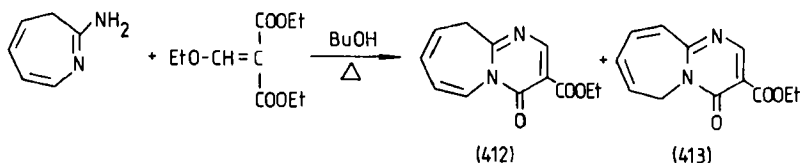
Chlorination of 3-(perhydroazepino)propionitrile (**408**) at temperatures up to 150°C and subsequent distillation *in vacuo* afforded perchlorinated pyrimido[1,2-*a*]azepine (**409**) (70LA45). In addition to hexachloro-1,8-naphthyridine (**411**), the perchloropyrimidoazepine **409** was obtained in 3–14% yield in the chlorination of 3-piperidinopropionitriles **410** (72GEP2024908).



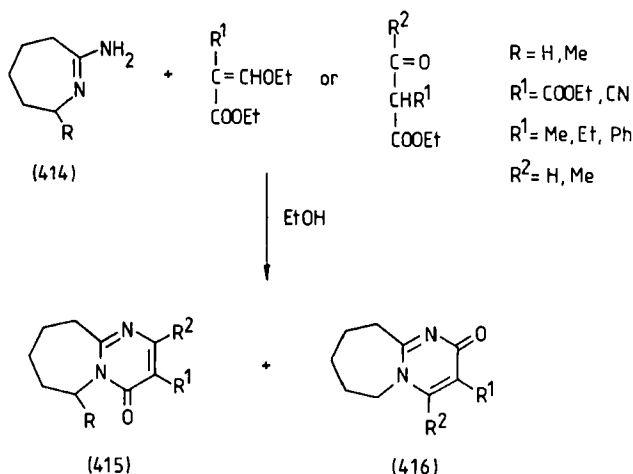
The reaction of 2-amino-3*H*-azepine with diethyl ethoxymethylenemalonate in boiling butanol for 1 hr gave a 6:1 mixture of ethyl 4-oxo-4*H*, 10*H*-pyrimido[1,2-*a*]azepine-3-carboxylate (**412**) and ethyl 4-oxo-4*H*, 6*H*-pyrimido[1,2-*a*]azepine-3-carboxylate (**413**) (84H2285).

The 4*H*, 6*H*-pyrimido[1,2-*a*]azepinone **413** is produced from the primarily formed 4*H*, 10*H*-isomer (**412**) in a symmetry-allowed [1,5]-sigmatropic shift.

Cyclocondensation of 2-amino-4,5,6,7-tetrahydro-3*H*-azepine (**414**) (*R* = *H*) with ethoxymethylenemalonate, (ethoxymethylene)cyanoacetate, 2-formyl esters, or 3-oxo esters afforded isomeric mixtures of the 4-oxo- (**415**,

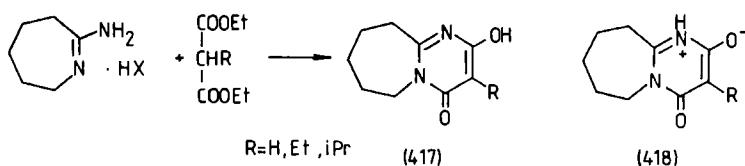


R = H) and 2-oxopyrimido[1,2-*a*]azepines (**416**) (81BEP883216; 82JHC909; 82MI2). The 7-methyl derivative (R = Me) of the amidine **414** gave only the 4-oxo isomer (**415**) (R = Me, R<sup>1</sup> = COOEt, R<sup>2</sup> = H) with diethyl ethoxymethylenemalonate, probably due to the steric hindrance effect of the methyl group on the ring nitrogen (82JHC909; 82MI2).



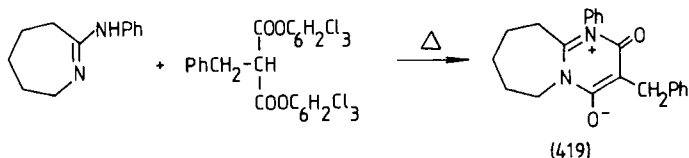
Researchers in Japan isolated only the 4-oxo isomers (**415**) (R = H, Ph; R<sup>1</sup> = COOEt, CN; R<sup>2</sup> = H) from reaction mixtures of amidines **414** (R = H, Ph) and ethoxymethylenemalonate or (ethoxymethylene)cyanoacetate (73JAP(K)34897; 76MIP10021).

Cyclocondensation of the sulfate salt of 2-amino-4,5,6,7-tetrahydro-3*H*-azepine with diethyl malonates in boiling ethanolic sodium ethoxide afforded 2-hydroxy-4-oxo derivatives **417** (61ZOB189; 73GEP2245386;

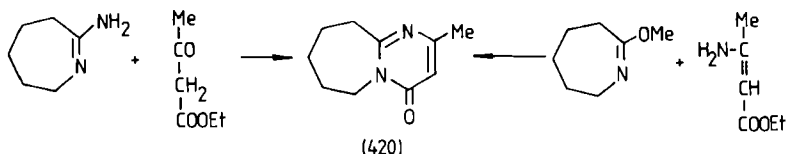


75FRP2197513). The high melting points of **417** and **424** (see later) suggest that their structures might involve zwitterionic forms (**418** and of the type of **419**).

The reaction of 2-phenylamino-4,5,6,7-tetrahydro-3*H*-azepine with bis(2,4,6-trichlorophenyl)benzylmalonates yielded the mesomeric betaine **419** (83TL4669).

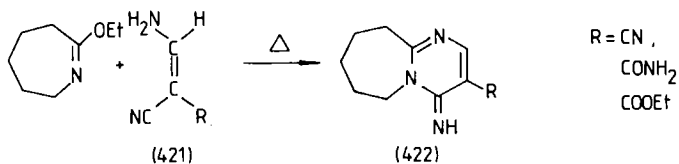


2-Methylhexahydropyrimidoazepin-4-one (**420**) was obtained both in the reaction of amidine hydrogen sulfate **414** ( $R = H$ ) with ethyl acetoacetate in ethanolic sodium ethoxide, and in the reaction of caprolactim methyl ether with ethyl 3-aminocrotonate in boiling ethanol (61ZOB189).



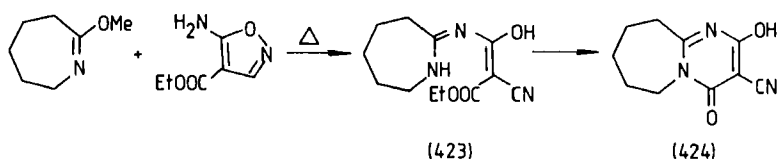
Agata *et al.* reacted caprolactim ethers with diethyl ethoxymethylene-malonate in the presence of ammonium acetate and obtained 4-oxopyrimido[1,2-*a*]azepine-3-carboxylate **415** ( $R = R^2 = H$ ,  $R^1 = COOEt$ ) (73JAP(K)34897; 76MIP10021). The reaction of caprolactim methyl ether with diethyl aminomethylenemalonate also gave 4-oxopyrimido[1,2-*a*]azepine-3-carboxylate **415** ( $R = H$ ,  $R^1 = COOEt$ ,  $R^2 = H$ ).

By refluxing caprolactim ethyl ether and aminomethylene derivatives **421** in alcohol, Brown and Ienage prepared 4-iminohexahydropyrimido[1,2-*a*]azepinones **422** in 71–88% yields (75AJC119).

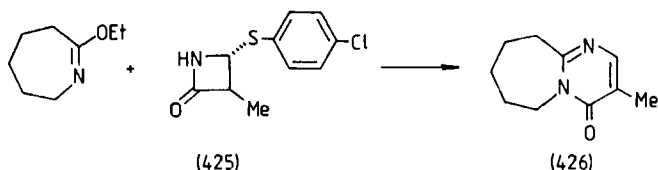


2-[(1-Hydroxy-2-ethoxycarbonyl)-2-cyanovinyl]imino]perhydroazepine (**423**), obtained from ethyl 5-aminoisoxazole-4-carboxylate and caprolactim

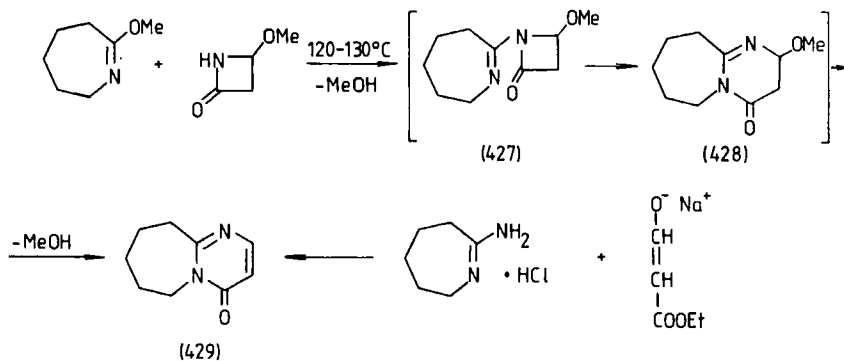
methyl ether, was cyclized to pyrimido[1,2-*a*]azepinone **424** by the action of aqueous sodium hydroxide solution at ambient temperature (69CB2739).



Caprolactim ethyl ether and 3-methyl-4-(*p*-chlorophenyl)thio-2-azetidinone (**425**) were reacted at 120–130°C for 3 hr to give the 3-methyl derivative **426** in 76% yield (73CPB1305).



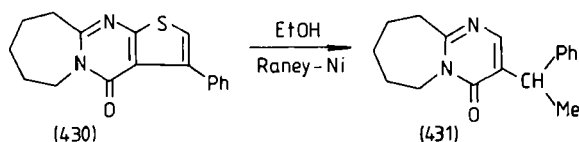
Bormann reacted caprolactim methyl ether with 4-methoxy-2-azetidinone at 120–130°C and obtained hexahydropyrimido[1,2-*a*]azepin-4-one (**429**) (74CB270).



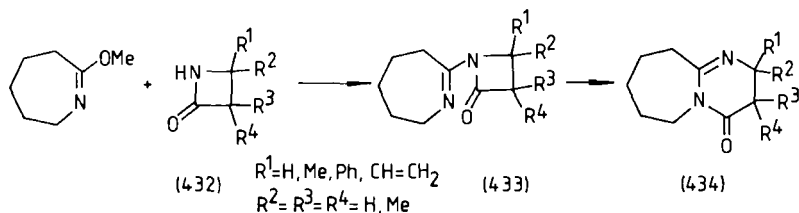
The primarily formed azetidinone derivative **427** isomerized to the octahydropyrimido[1,2-*a*]azepin-4-ones **428** above 130°C (70CB1797); Compound **429** was also obtained in the reaction of 2-amino-3*H*-4,5,6,7-tetrahydroazepine hydrochloride (**414**·HCl; R = H) and the sodium salt of ethyl formylacetate (83JOC2914).

Shvedov *et al.* prepared the hexahydropyrimido[1,2-*a*]azepinone **431** by the desulfuration over Raney nickel of the tricyclic compound **430**.

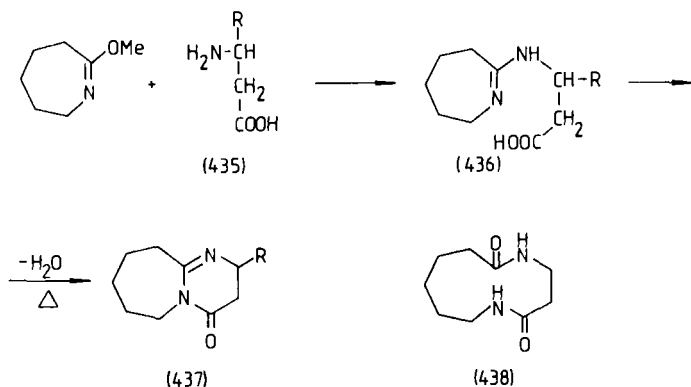
Compound **430** was obtained in the reaction of caprolactam and ethyl 2-amino-4-phenylthiophene-3-carboxylate (75KGS765).



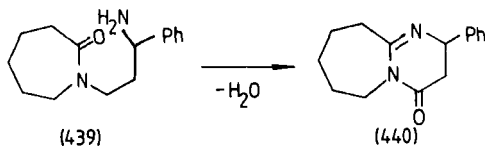
The reaction of caprolactim methyl ether with azetidinones **432** gave octahydropyrimido[1,2-*a*]azepin-4-ones **434** above 130°C (70CB1797; 70GEP1803785). The condensation products **433** could sometimes be isolated. They were then cyclized to octahydropyrimido[1,2-*a*]azepinones **434** thermally under nitrogen above 180°C, or in the presence of methanolic sodium methylate in methylene chloride under reflux conditions (70CB1797).



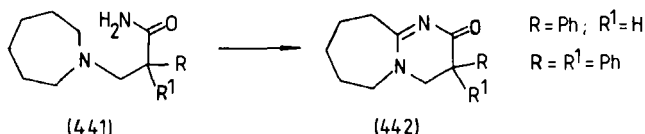
The condensation products **436** of 3-aminopropionic acids **435** and caprolactim methyl ether were cyclized to octahydropyrimido[1,2-*a*]azepin-4-ones **437** on heating in dichlorobenzene under a water condenser (59LA166; 61GEP1082268; 65JPR18; 65T3537; 65ZOB2231). Starting from the amino acid **435** ( $R = \text{H}$ ), the cyclopeptide **438** was isolated from the reaction mixture in 12% yield in addition to the main product **437** ( $R = \text{H}$ ) (65ZOB2231).



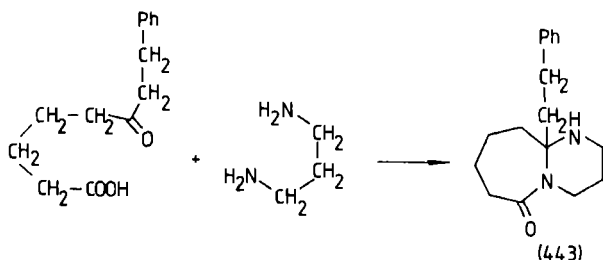
2-Phenyloctahydropyrimido[1,2-*a*]azepine (**440**) was prepared from the caprolactam derivative **439** by vacuum distillation in the presence of *p*-toluenesulfonic acid (73AP325).



Möhrle and Hemmerling oxidized the propionamides **441** with mercury(II) acetate-EDTA (EDTA = ethylenediaminetetraacetate) reagent to obtain octahydropyrimido[1,2-*a*]azepin-2-ones **442** (77AP200).



The perhydropyrimido[1,2-*a*]azepin-6-one **443** was obtained by heating 6-oxo-8-phenyloctanoic acid and 1,3-diaminopropane in the presence of *p*-toluenesulfonic acid in toluene under a water condenser (68USP3334099; 69USP3454585).

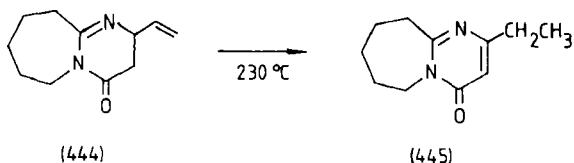


## 2. Reactions

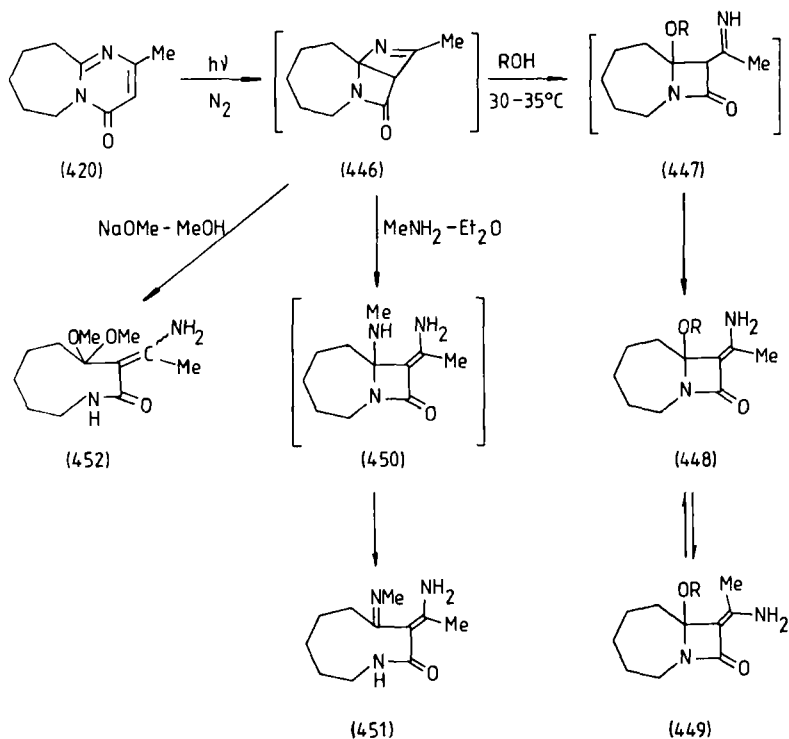
On standing in water at ambient temperature for 2 days, octahydropyrimido[1,2-*a*]azepin-4-one **437** (R = H) gave a mixture of the acid **436** (R = H) and the cyclopeptide **438** (65T3537; 65ZOB2231).

2-Vinyloctahydropyrimido[1,2-*a*]azepinone (**444**) was isomerized thermally to the 2-ethylhexahydro derivative (**455**) at 230°C (74CB270).

In addition to those of other monocyclic and bicyclic pyrimidinone derivatives, photolysis of hexahydropyrimido[1,2-*a*]azepin-4-ones was



studied by Nagata, Yamazaki, and co-workers (79JOC2083; 80TL3067; 81JOC1769; 83JOC2914). Irradiation of 2-methylhexahydropyrimido-[1,2-*a*]azepin-4-one (**420**) in alcoholic solution gave the azabicyclo-[5.2.0]nonanone **448** (79JOC2083). As electrocyclic reactions of cisoid diene systems in excited states are symmetry allowed for the disrotatory mode of ring closure, it was assumed that in the first step a Dewar-type pyrimidinone (**446**) was formed. Later, the presence of a Dewar-type pyrimidinone in the reaction mixture was detected by  $^{13}\text{C}$  NMR at under  $-10^\circ\text{C}$  in the case of monocyclic pyrimidinones (81JOC1769; 83JOC2914). The existence of the imine **447** was postulated, as **448** in solution gave an isomeric mixture of **448** and **449** (79JOC2083) (Scheme 7). When the



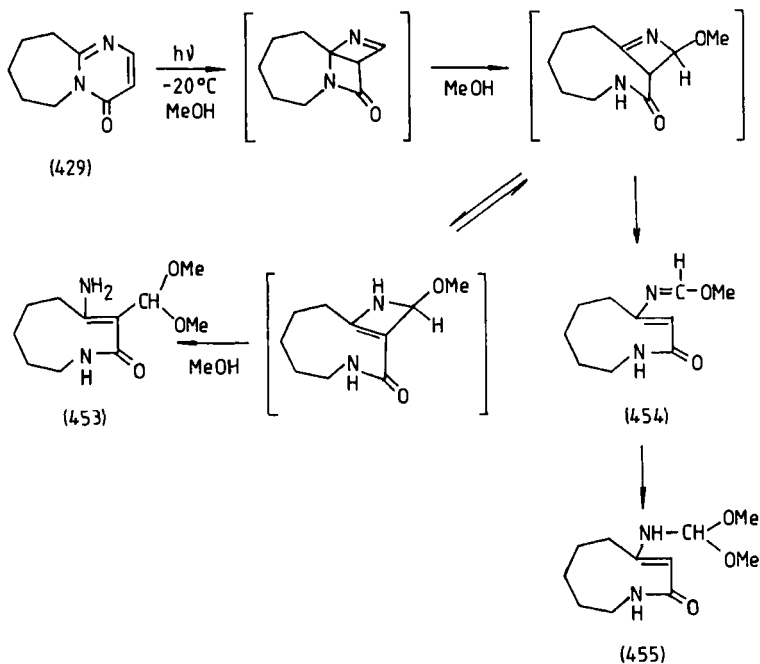
SCHEME 7



photolysis of pyrimido[1,2-*a*]azepinone **420** was carried out in a mixture of methylamine and diethyl ether, the nine-membered lactam **451** was obtained from intermediate **450** in 22.4% yield (80TL3067), while in methanolic sodium methoxide (0.85 *M*) the ketal derivative **452** was isolated in 41% yield (81JOC1769).

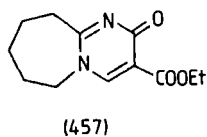
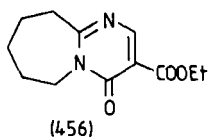
The photochemical rearrangement of hexahydropyrimido[1,2-*a*]azepin-4-one (**429**) in methanol afforded the nine-membered lactams **453**–**455**, either in the presence or in the absence of sodium methylate (Scheme 8) (83JOC2914).

Catalytic hydrogenation of a mixture of esters **412** and **413** gave ethyl hexahydropyrimido[1,2-*a*]azepine-3-carboxylate (**456**) (84H2285).

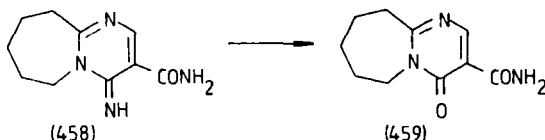


SCHEME 8

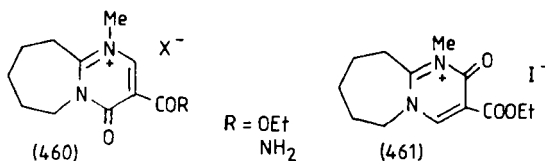
Carboxylic acids, amides, and hydrazides were prepared from esters **412**, **456**, and **457** (77MI1; 81BEP883216; 84H2285).



Alkaline hydrolysis of 4-iminopyrimidoazepine-3-carboxamide (**458**) gave the 4-oxo derivative **459** in 81% yield at pH 10 (75AJC119). In contrast to their higher homologues, 4-iminopyrimido[1,2-*a*]azepines **422** did not undergo the Dimroth rearrangement on prolonged boiling in butanol or in warm alkaline medium.

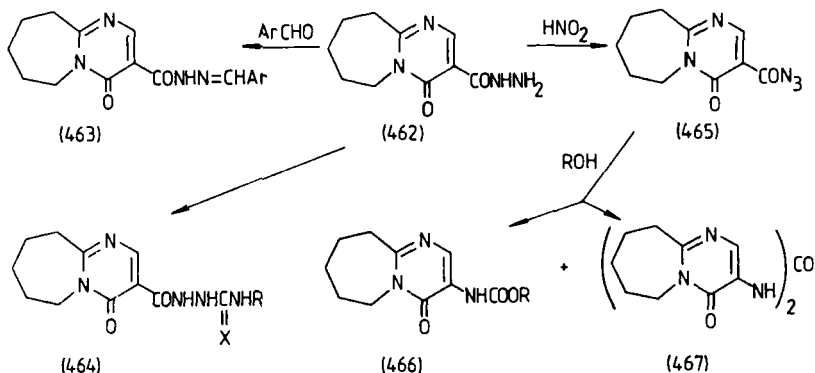


Quaternization of esters **456** and **457** and amide **459** with methyl iodide and dimethyl sulfate gave the corresponding quaternary salts **460** and **461** (73JAP(K)34897; 76MIP10021; 81BEP883216).



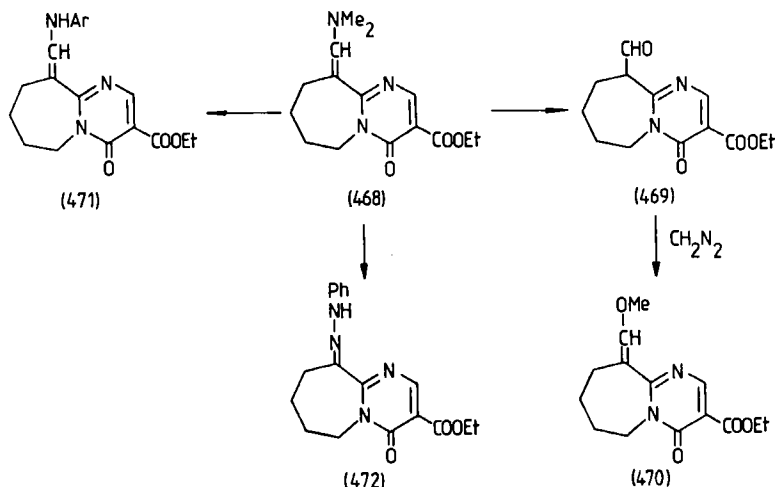
The 3-carbazoyl group of pyrimido[1,2-*a*]azepine **462** was acylated at N-2 with benzoyl chloride, or reacted with aldehydes, isocyanates, or isothiocyanates (77MI1). 3-Bromohexahydropyrimido[1,2-*a*]azepin-4-one was obtained from the 3-carboxylic acid **415** ( $R = R^2 = H$ ,  $R^1 = COOH$ ) in the Hunsdicker reaction.

The azide **465**, obtained from the hydrazide **462** with sodium nitrite in 50% acetic acid, afforded the carbamates **466** in refluxing alcohol. The presence of traces of water resulted in the formation of the urea **467** as by-product.



Deuteration experiments revealed that the 2-oxo ester **457** contains a more active methylene group in position-10 than does the 4-oxo isomer **456** (82JHC909; 82MI2).

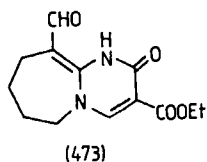
Vielsmeier-Haack formylation of ethyl hexahydropyrimido[1,2-*a*]-azepine-3-carboxylate (**456**) with the complex of phosphoryl chloride and dimethylformamide led to the dimethylaminomethylene derivative **468**, which was then hydrolyzed to the formyl derivative **469** (85JCS(P2)1873).



Treatment of the formyl derivative **469** with diazomethane in chloroform gave the methoxymethylene derivative **470** in 39% yield (85JCS(P2)1873).

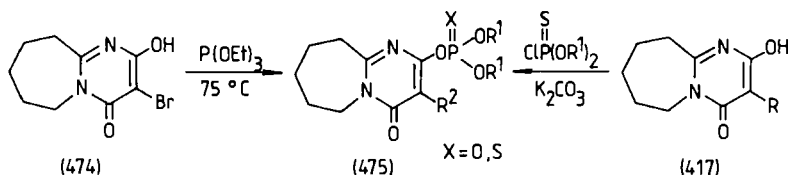
The dimethylaminomethylene compound **468** was converted to arylaminomethylene derivatives **471** with anilines in acetic acid, and to the phenylhydrazone **472** with phenyldiazonium chloride (83JCR(S)161; 84JMC1253). The ester group of compounds **471** and **472** could be hydrolyzed to a carboxylic group under alkaline conditions (84JMC1253).

The formyl derivative **473** was prepared from the 2-oxo derivative **457** with phosphoryl chloride and dimethylformamide under milder conditions than required to prepare the 4-oxo derivative **469** from **456** (85JCS(P2)1873).

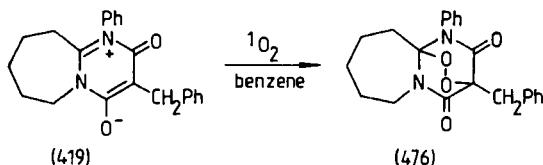


Bromination of pyrimido[1,2-*a*]azepinone **417** (R = H) with *N*-bromosuccinimide in methanol yielded the 3-bromo derivative **474**, which was converted

to the 2-diethoxyphosphoryloxy derivative **475** ( $R = H$ ,  $R^1 = Et$ ,  $X = O$ ) with triethyl phosphite at  $75^\circ C$  (73GEP2245386; 75FRP2197513). Compounds **475** ( $R^1 = Me, Et$ ;  $R^2 = H, i-Pr$ ;  $X = S$ ) were also obtained from pyrimidoazepinones **417** ( $R = H, i-Pr$ ) with dialkyl chlorothiophosphates in the presence of potassium carbonate in acetonitrile.



The mesomeric betaine **419** underwent 1,4-dipolar cycloaddition with photochemically generated singlet oxygen in benzene at  $5^\circ C$  to give the stable peroxide **476** in 94% yield (83TL4669).

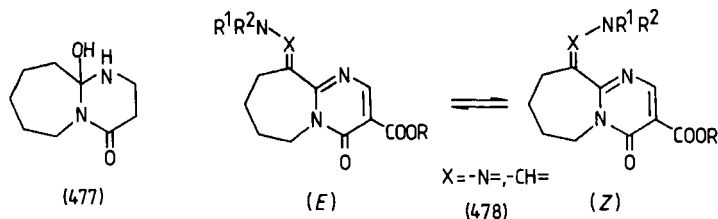


### 3. Physicochemical Properties

The following spectral data are available: for 2,3,4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepine, IR (73AP325); for pyrimido[1,2-*a*]azepin-2-ones, UV (82JHC909; 82MI2; 85JCS(P2)1873), IR (77AP200; 82JHC909; 82MI2), and  $^1H$  NMR (77AP200; 82JHC909; 82MI2; 85JCS(P2)1873); for pyrimido[1,2-*a*]azepin-4-ones, UV (61ZOB189; 73JAP(K)34897; 75AJC119; 76MIP10021; 82JHC909; 82MI2; 83JCS(P2)1409; 84H2285; 85JCS(P2)1873), IR (65T3537; 65ZOB2231; 69CB2739; 70CB1797; 73AP325; 73CPB1305; 73GEP2245386; 73JAP(K)34897; 74CB270; 75FRP2197513; 76MIP10021; 82JHC909; 82MI2; 83TL4669; 84H2285),  $^1H$  NMR (69CB2739; 73CPB1305; 74CB270; 75AJC119; 82JHC909; 82MI2; 83JCR(S)161; 83JCS(P2)1409; 85JCS(P2)1873; 85JCS(P2)1881),  $^{13}C$  NMR (83JCR(S)161; 83JCS(P2)1409; 84H2285; 85JCS(P2)1881) and  $^{15}N$  NMR (85JCS(P2)1881); and for 4-iminopyrimido[1,2-*a*]azepines, UV, IR, and  $^1H$  NMR (75AJC119).

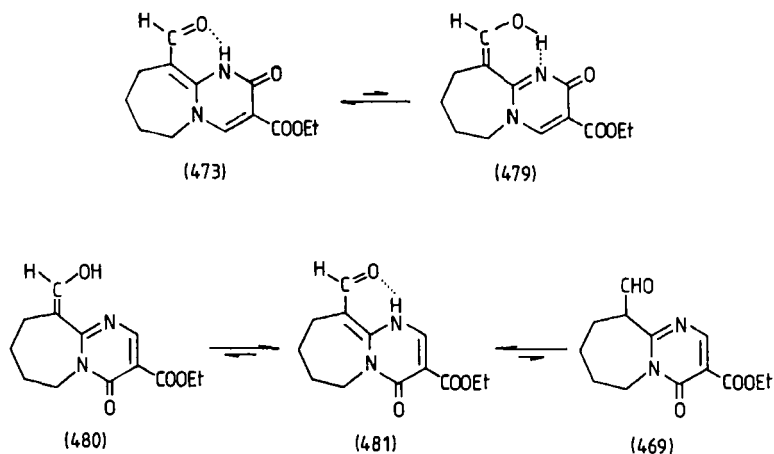
The  $pK_a$  values of 4-iminopyrimido[1,2-*a*]azepines **422** and 4-oxocarboxamide **459** were determined by UV spectroscopy (75AJC119).

The mass spectral behavior of the cyclopeptide **438** shows the formation of the azacyclol structure **477** in a mass spectrometer (65ACH(44)93; 68ZOB770).



10-(Aminomethylene)- ( $X = CH=$ ) and 10-hydrazonopyrimido[1,2-*a*]-azepinones ( $X = N=$ ) (**478**) exhibit a solvent-dependent (E)–(Z) isomerism (83JCR(S)161; 83JCS(P)1409; 84JMC1253).

The 2-oxo formyl derivative **473** exists as a tautomeric mixture of **473** and **479**, with a predominance of the former (85JCS(P)1873; 85JCS(P)1881). At the same time, the 4-oxo formyl isomer **469** exhibits triple tautomerism between forms **469**, **480**, and **481**.



#### 4. Applications

Certain pyrimido[1,2-*a*]azepines have been patented as antianginal (81BEP883216) and antiinflammatory compounds (68USP3334099; 69USP3454585), insecticides (73GEP2245386; 75FRP2197513), central nervous system depressants, and sedatives (68USP3334099; 69USP3454585).

Hexahydropyrimido[1,2-*a*]azepin-4-ones **456**, **463**, and **467** display analgetic activity (77MI1). 10-Aminomethylene and 10-phenylhydrazino derivatives **478** ( $R = H$ ) possess weak antiallergic effects in the passive cutaneous anaphylaxis (PCA) test (84JMC1253).

Perhydropyrimido[1,2-*a*]azepine has been patented as a dye fixing agent for the printing of cotton fabrics (79JAP(K)27078), as a catalyst for a phenolic resin modifier (80JAP(K)120622), and for room temperature-curable traffic paints (80JAP(K)133470).

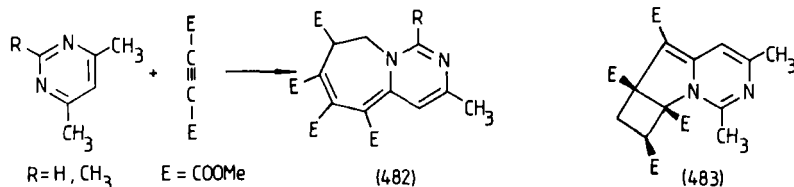
1-Benzylperhydropyrimido[1,2-*a*]azepine dihydrochloride has been applied as a vulcanization accelerator for fluoro rubber (77JAP(K)15543).

### III. Pyrimido[1,6-*a*]azepines

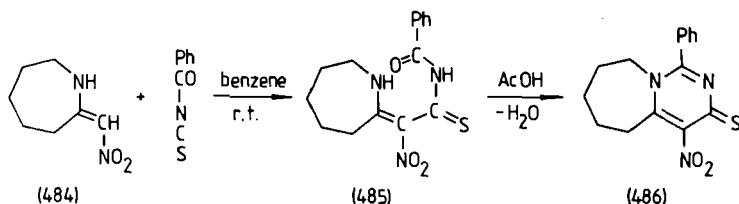
#### A. SYNTHESIS

During a study of the reaction between dimethyl acetylenedicarboxylate and aromatic nitrogen heterocycles containing activated methyl groups, Acheson *et al.* obtained 2:1 adducts in low yields from 4,6-dimethyl- and 2,4,6-trimethylpyrimidines in refluxing acetonitrile (68JCS(C)926).

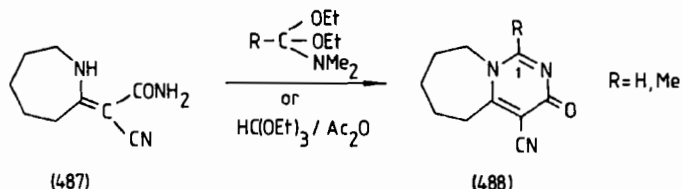
The pyrimido[1,6-*a*]azepine structure **482** was attributed to both products, but the structure of the product obtained from 2,4,6-trimethylpyrimidine was later corrected to the tricyclic derivative **483** (77JCS(P)1924).



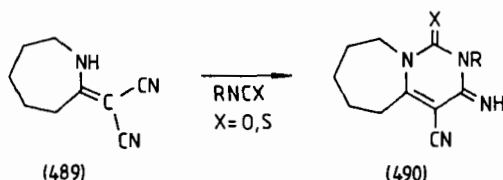
Rajappa *et al.* obtained pyrimido[1,6-*a*]azepinethione **486** when addition product **485**, prepared from nitroolefin **484** and benzoyl isothiocyanate in benzene at ambient temperature, was recrystallized from acetic acid (77IJC(B)297).



Granik *et al.* prepared pyrimido[1,6-*a*]azepin-3-ones **488** in good yields by the reaction of enamino amide **487** with diethyl acetals of dimethylformamide or dimethylacetamide in refluxing ethanol (80KGS1120). Compound **488** ( $\text{R} = \text{H}$ ) was also obtained from enamino amide **487** in 61% yield by reacting it with triethyl orthoformate in refluxing acetic anhydride.



Ebeid and Bitter synthesized pyrimido[1,6-*a*]azepine derivatives **490** by reacting 2-(dicyanomethylene)perhydroazepine (**489**) with isocyanates and isothiocyanates (78MI5).



## B. REACTIONS

The pyrimidone ring of pyrimido[1,6-*a*]azepin-3-ones **488** is sensitive to nucleophilic attack at position 1. Compound **488** (R = H) gave azepine derivative **487** when heated with *p*-phenylethylamine or in a basic buffer solution (80KGS1120).

Hydrogenation of 8,9-dihydropyrimido[1,6-*a*]azepine **482** (R = H) in methanol over palladium-on-charcoal (10%) catalyst under 5 atm of hydrogen afforded the 1,2,8,9-tetrahydro derivative **491** (68JCS(C)926).



Whereas the five- and six-membered homologues **492** (n = 1, 2) contain a reactive methylene group which could be deuterated in perdeuteroacetic acid, the seven-membered pyrimido[1,6-*a*]azepinone **492** (n = 3) did not undergo hydrogen  $\rightarrow$  deuterium exchange under similar conditions (82KGS518).

## C. SPECTROSCOPIC PROPERTIES

UV (68JCS(C)926; 80KGS1120), IR (68JCS(C)926),  $^1\text{H}$ -NMR (68JCS(C)926; 80KGS1120), and mass spectral (68JCS(C)383; 80KGS1120) data are available for different pyrimido[1,6-*a*]azepines.

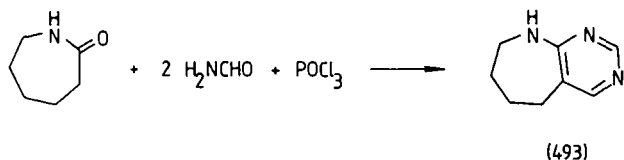
## D. APPLICATIONS

3,4,4a,5,6,7,8,9-Octahydropyrimido[6,1-*a*]azepine has been patented as a corrosion inhibitor component for the stabilization of photographic baths (79GEP2720111).

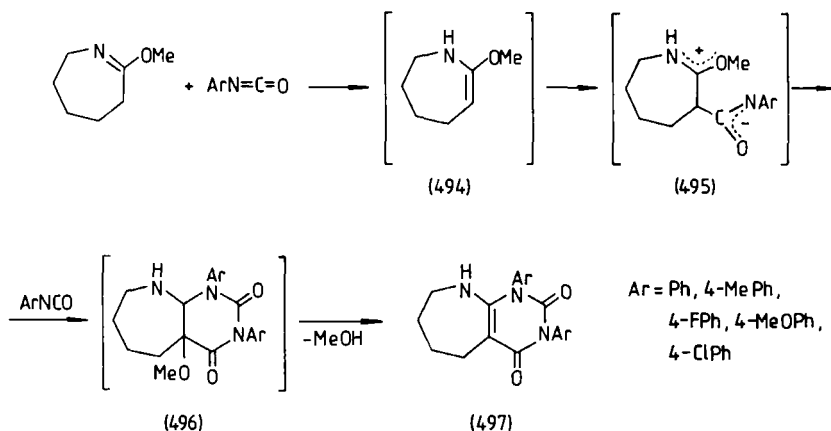
IV. Pyrimido[4,5-*b*]azepines

## A. SYNTHESIS

The reaction of caprolactam with a mixture of formamide and phosphoryl chloride in a sealed tube at 120°C for 12 hr afforded 6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*]azepine (**493**) in 7% yield (70TL861; 73BCJ2835).



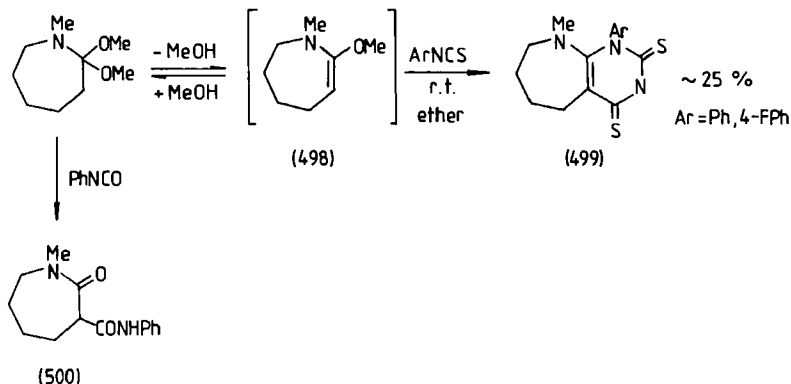
Pyrimido[4,5-*b*]azepine-2,4-diones **497** were prepared in 12–38% yield by reacting caprolactam methyl ether with aryl isocyanates at 150–155°C for 3–5 hr (73CB374). It was suggested that a ketene-*O,N*-acetal was first formed, which reacted with isocyanates via the 1,4-dipole form **495**. In the final step, pyrimido[4,5-*b*]azepine-2,4-diones **497** were formed from perhydro-pyrimido[4,5-*b*]azepines **496** by the elimination of methanol.



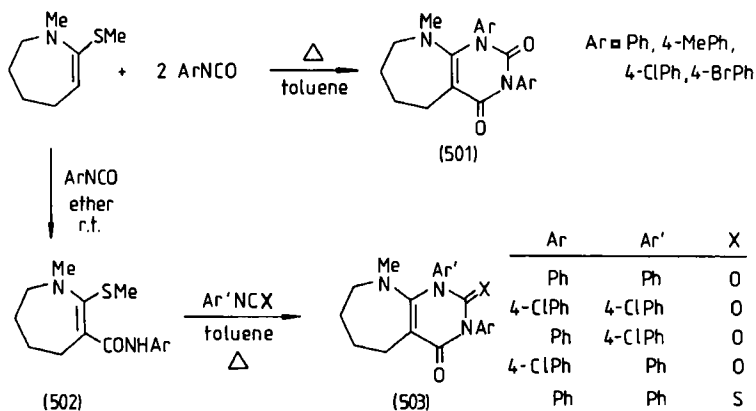
In the reaction of *N*-methylcaprolactam acetal and phenyl isothiocyanate, ketene-*O,N*-acetal **498** was considered to be the reactive species (80IJC(B)195).



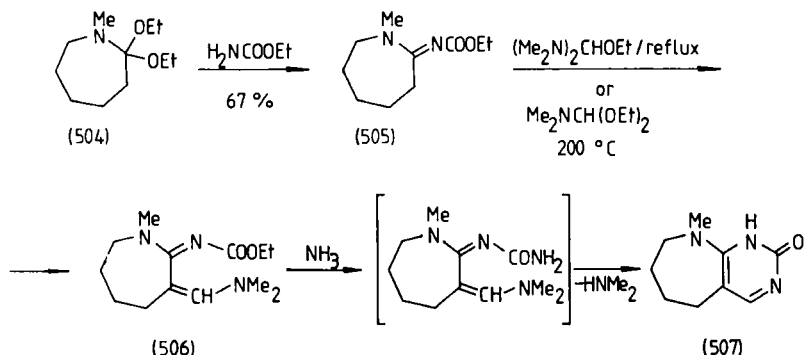
The *N*-methyl derivative **498** reacted in a similar way as **494** to give pyrimido[4,5-*b*]azepine-2,4-dithiones **499**. Under similar conditions, only the 2-oxoperhydroazepine-3-carboxamide **500** was obtained with phenyl isocyanate.



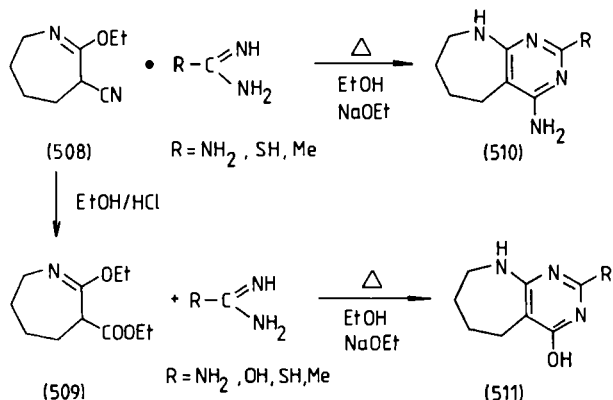
When aryl isocyanates were reacted with 1-methyl-2-methylthio-4,5,6,7-tetrahydro-1*H*-azepine in refluxing toluene for 15 hr, pyrimido[4,5-*b*]azepine-2,4-diones **501** were obtained in 54–71% yields (82H413; 82S156; 85CPB4299). Pyrimido[4,5-*b*]azepin-2,4-dione **501** (Ar = Ph) was also prepared in 55% yield from 1-methyl-2-methoxy-4,5,6,7-tetrahydro-3*H*-azepinium methosulfate with phenyl isocyanate in dichloromethane at room temperature (80IJC(B)195). Reaction between aryl isocyanates and 1-methyl-2-methylthio-4,5,6,7-tetrahydro-1*H*-azepine in diethyl ether at ambient temperature gave azepine-3-carboxamides **502**, from which pyrimido[4,5-*b*]azepin-2,4-diones **503** containing different aromatic nuclei in positions 1 and 3 were obtained with aryl iso(thio)cyanates in boiling toluene (82H413; 85CPB4299).



Pyrimido[4,5-*b*]azepin-2-one **507** was prepared in 36% yield as a 1:1 adduct with urea from azepine derivative **506** with alcoholic ammonia solution in a sealed tube at 180°C for 6 hr (82KG51553). Compound **506** was obtained from *N*-methylcaprolactam acetal (**504**) in two steps, through intermediates **505**.

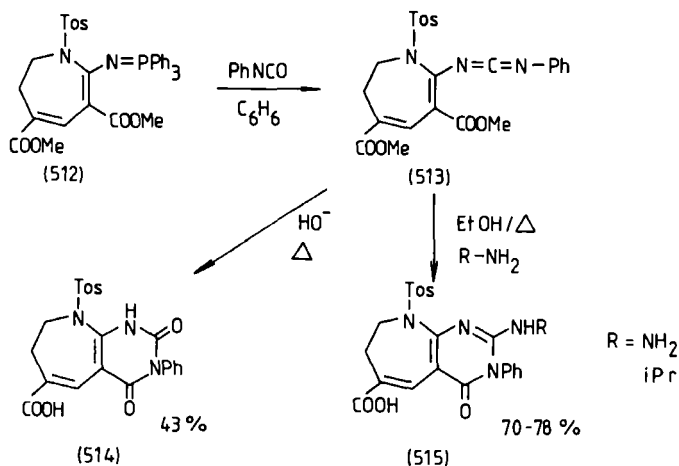


Cyclocondensation of 3-cyano- and 3-ethoxycarbonyl-2-ethoxy-4,5,6,7-tetrahydro-3*H*-azepines (**508** and **509**) with compounds containing an amidine moiety in boiling ethanol in the presence of sodium ethoxide afforded 2-substituted 4-amino- (**510**) and 4-hydroxypyrimido[4,5-*b*]azepines (**511**) (67M11; 68MIP196863). The application of thiourea and guanidine gave higher yields (43–91.6%) than with acetamidine and urea (4.7–26.3%) (67M11).



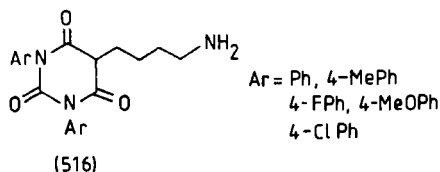
Wamhoff and Hendrixx prepared pyrimido[4,5-*b*]azepine-6-carboxylic acid derivatives **514** and **515** from carbodiimide **513** by reacting it with 5% sodium hydroxide solution or with hydrazine and *i*-propylamine in boiling

ethanol for 3 hr (85CB863). Carbodiimide **513** was obtained from reaction of **512** with phenyl isocyanate in benzene.



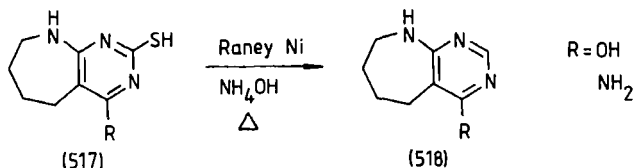
## B. REACTIONS

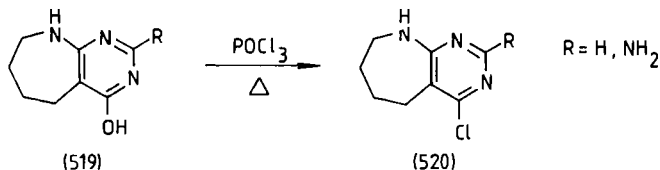
By heating in 10% hydrochloric acid, pyrimido[4,5-*b*]azepine-2,4-diones **497** were hydrolyzed to 5-(4-aminobutyl)-1,3-diarylbarbituric acids **516** in 70–88% yields (73CB374).



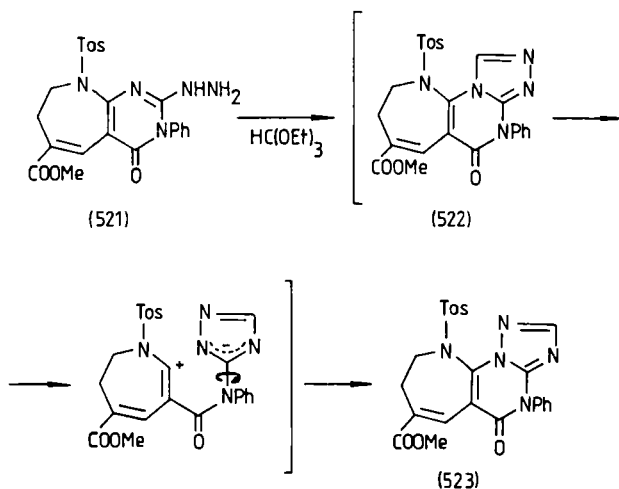
2-Mercaptopyrimido[4,5-*b*]azepines **517** were desulfurized to **518** by heating in aqueous ammonium hydroxide solution in the presence of Raney nickel for 3 hr, with 70–81% yields (67MI1).

The treatment of 4-hydroxypyrimido[4,5-*b*]azepines **519** with phosphoryl chloride in the presence of *N,N*-diethylaniline gave the 4-chloro derivatives **520** in 65–85% yields (67MI1).





Triazolo [2',3':1,2]pyrimido[4,5-*b*]azepine (**523**) was obtained in 83% yield from 2-hydrazinopyrimido[4,5-*b*]azepine **521** by heating with triethyl orthoformate for 3 hr (85CB863). It was suggested that the isomeric triazolo [4',3':1,2]pyrimido[4,5-*b*]azepine (**522**) was first formed, which then underwent a Dimroth rearrangement to give **523**.



### C. SPECTROSCOPIC PROPERTIES

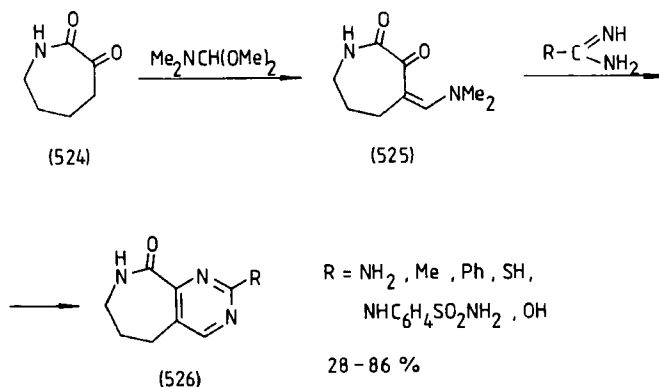
The following types of spectroscopic data can be found in the literature on pyrimido[4,5-*b*]azepines: UV (67MI1; 70TL861; 73BCJ2835; 82H413; 82S156; 85CB863), IR (82H413; 82S156; 85CB863; 85CPB4299), <sup>1</sup>H-NMR (73BCJ2835; 801JC(B)195; 82H413; 82S156; 85CB863; 85CPB4299), and mass spectral data (82H413; 85CPB4299).

The UV spectra of pyrimido[4,5-*b*]azepines are very similar to those of the corresponding 4-aminopyrimidines (67MI1).

The mass spectra of pyrimido[4,5-*b*]azepines **501** and **503** show a characteristic fragmentation peak  $[\text{M} - \text{ArNCO}]^+$  due to retro Diels-Alder decomposition (82H413; 85CPB4299).

## V. Pyrimido[4,5-*c*]azepines

The first pyrimido[4,5-*c*]azepines were prepared by Glushkov *et al.*, starting from perhydroazepine-2,3-dione (**524**). Aminomethylene derivative **525** was obtained from **524** with dimethylformamide dimethyl acetal, and was then reacted in refluxing ethanol with compounds containing an amidine moiety to give pyrimido[4,5-*c*]azepines **526** in 28–86% yields (75MI1; 76KGS1640).

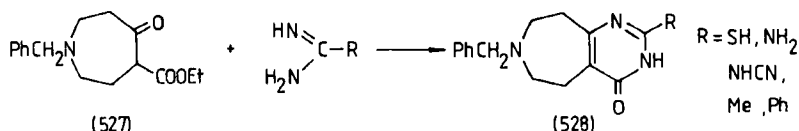


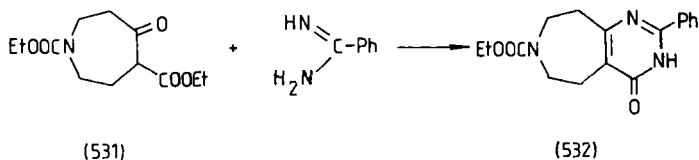
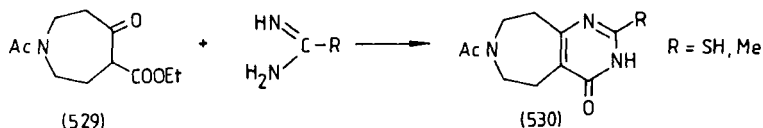
## VI. Pyrimido[4,5-*d*]azepines

Yamamoto *et al.* studied the synthesis and reactivities of pyrimido[4,5-*d*]azepines (71BCJ153; 77BCJ453; 78H275).

### A. SYNTHESIS

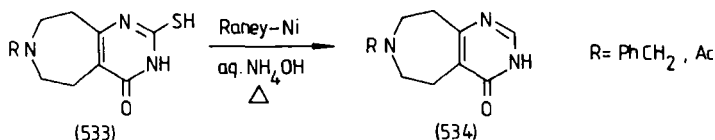
The cyclocondensation of 5-ethoxycarbonylazepin-4-ones **527**, **529** and **531** with compounds containing an amidine moiety in boiling ethanol in the presence of sodium ethoxide afforded 2,7-disubstituted hexahydro-3*H*-pyrimido[4,5-*d*]azepin-4-ones **528**, **530** and **532** in 24–70% yields (71BCJ153; 77BCJ453; 78H275).



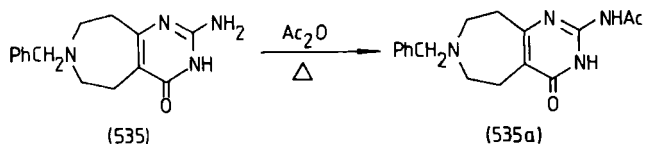


## B. REACTIONS

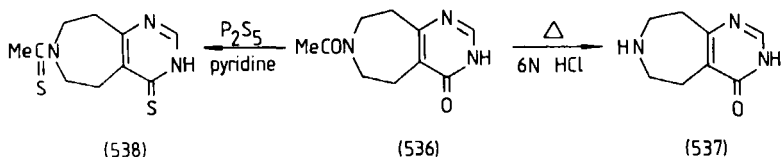
The 2-mercapto derivatives **533** were desulfurized by heating in aqueous ammonium solution in the presence of Raney nickel to yield 2-unsubstituted pyrimido[4,5-*d*]azepines **534** in 85% yield (71BCJ153).



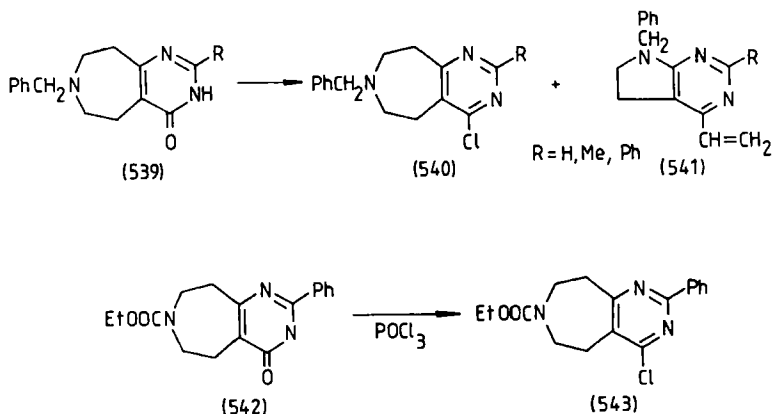
The 2-amino derivative **535** was acylated by heating in acetic anhydride for 10 hr to afford the 2-acetamido compound **535a** in 68% yield.



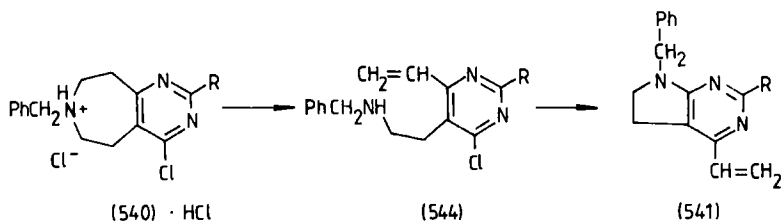
Heating the 7-acetyl derivative **536** in 6 *N* hydrochloric acid gave the deacetylated bicycle **537** in 97% yield. The reaction of **536** with phosphorus pentasulfide in boiling pyridine for 0.5 hr afforded the bis(sulfurated) derivative **538** in 71% yield (71BCJ153).



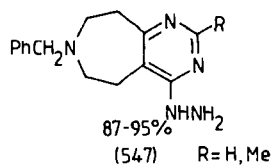
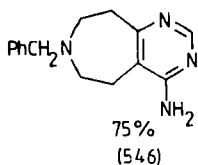
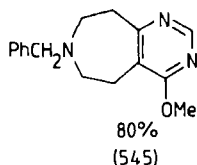
Treatment of pyrimido[4,5-*d*]azepin-4-ones **539** and **542** with phosphoryl chloride in the presence of *N,N*-diethylaniline as catalyst afforded 4-chloropyrimido[4,5-*b*]azepines **540** and **543** in 76–81% yields (71BCJ153; 77BCJ453; 78H275). If a longer reaction time was applied in the absence of *N,N*-diethylaniline, products **541** were also isolated in 20–45% yields after rearrangement and elimination of hydrogen chloride (77BCJ453). The same products **541** were obtained by heating the chloro compounds **540** in phosphoryl chloride or the hydrochloride salts of **540** in dimethylformamide.



For the reaction mechanism it was suggested that the hydrochloride salts of **540** suffered Hofmann elimination to give pyrimidines **544**. The 4-chloro-5-[(2-benzylamino)ethyl]pyrimidines **544** then underwent cyclization to pyrrolo[2,3-*d*]pyrimidines **541** (77BCJ453). The moderate yields of **541** were due to the presence of the 4-vinyl group.

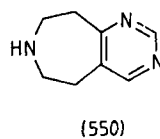
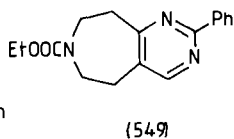
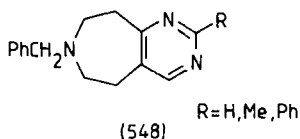


The 4-chloro atom in pyrimido[4,5-*b*]azepines **540** can be substituted by a 4-methoxy, a 4-amino, or a 4-hydrazino group with sodium methoxide in refluxing methanol, ethanolic ammonia solution in a sealed tube at 130°C, or hydrazine hydrate in boiling ethanol to yield **545–547** (71BCJ153).



The oxidation of 4-hydrazinopyrimido[4,5-*b*]azepines **547** with silver oxide in boiling methanol for 2 hr gave 4-unsubstituted derivatives **548** in 63–83% yields (71BCJ153).

4-Unsubstituted pyrimido[4,5-*b*]azepines **548** (R = H, Ph) and **549** were also prepared from the corresponding 4-chloro derivatives **540** (R = H, Ph) and **543** by catalytic reduction over 10% palladium-on-carbon catalyst in alcoholic solution in the presence of a base (71BCJ153; 78H275).

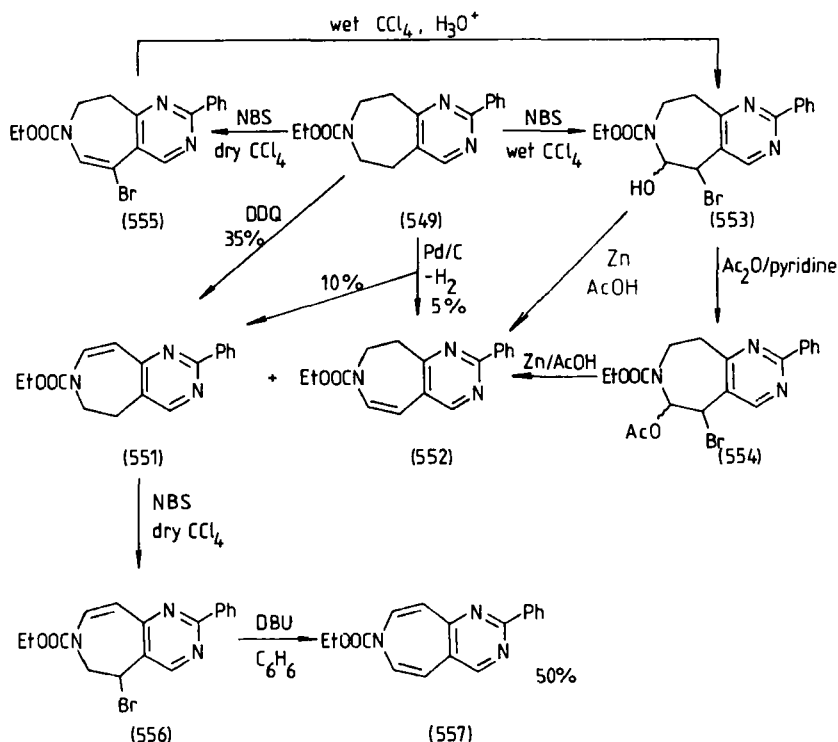


The catalytic debenzylation of 7-benzyl-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*d*]azepine **548** (R = H) was carried out in ethanolic solution in the presence of traces of acetic acid over 10% palladium-on-charcoal catalyst to give unsubstituted tetrahydropyrimido[4,5-*d*]azepine (**550**) in 80% yield (71BCJ153).

Dehydrogenation of pyrimido[4,5-*d*]azepines **532**, **540** (R = Ph), **543**, and **548** (R = Ph) was unsuccessful over palladium-on-carbon catalyst in boiling decalin or with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in boiling dioxane. However, when pyrimido[4,5-*b*]azepine **549** was treated with palladium-on-carbon catalyst, dihydropyrimido[4,5-*b*]azepines **551** and **552** could be isolated chromatographically in 10 and 5% yields, respectively (78H275). When pyrimido[4,5-*b*]azepine **549** was heated in dioxane in the presence of DDQ, 5,6-dihydropyrimido[4,5-*d*]azepine **551** was the sole product, in 35% yield. 8,9-Dihydropyrimido[4,5-*d*]azepine **552** could be obtained in 50% overall yield when pyrimido[4,5-*d*]azepine **549** was treated with *N*-bromosuccinimide (NBS) in wet carbon tetrachloride, and the resulting bromohydrin **553** was reduced with zinc powder in acetic acid at 60°C. Acetylation of the bromohydrin with acetic anhydride in pyridine gave the more stable acetoxy derivative **554**.

Bromination of pyrimido[4,5-*d*]azepines **549** and **551** with NBS in dry carbon tetrachloride afforded the 5-bromo derivatives **555** and **556** (78H275).





SCHEME 9

5-Bromo-8,9-dihydropyrimido[4,5-*d*]azepine **555** could be converted to the bromohydrin **553** in wet carbon tetrachloride in the presence of catalytic amounts of acid. 5-Bromo-5,6-dihydropyrimido[4,5-*d*]azepine **556** was dehydrobrominated with DBU in benzene to give 7*H*-pyrimido[4,5-*b*]azepine (**557**).

### C. PHYSICOCHEMICAL PROPERTIES

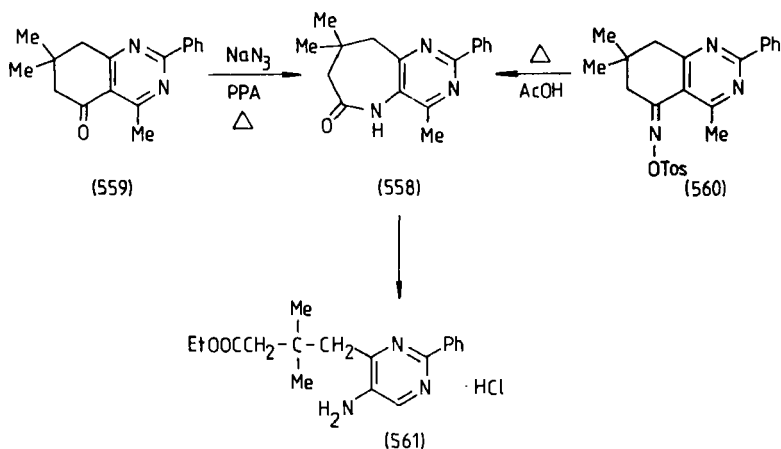
Pyrimido[4,5-*d*]azepines have been characterized by UV (71BCJ153; 77BCJ453), IR, <sup>1</sup>H-NMR (71BCJ153; 77BCJ453; 78H275), and mass spectroscopic (78H275) data.

Protonation of 6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*d*]azepines **540** and **548** occurred at N-7 (77BCJ453).

The protonation constants of pyrimido[4,5-*d*]azepines and **548** (R = H) have been determined (77BCJ453).

## VII. Pyrimido[5,4-*b*]azepines

Strakow *et al.* prepared 2-phenyl-4,8,8-trimethyl-5,7,8,9-tetrahydro-6*H*-pyrimido[5,4-*b*]azepine **558** by the Schmidt reaction of 2-phenyl-4,7,7-trimethyl-5,6,7,8-tetrahydrobenzo[*d*]pyrimidin-5-one (**559**) with sodium azide in polyphosphoric acid (PPA) and by Beckmann rearrangement of the tosyloxime derivative **560** in acetic acid, in 50% and 90% yields, respectively (72MI1; 73MI1). The ring-opened product **561** was obtained by heating the pyrimido[5,4-*b*]azepine **558** in ethanol containing hydrochloric acid (73MI1).



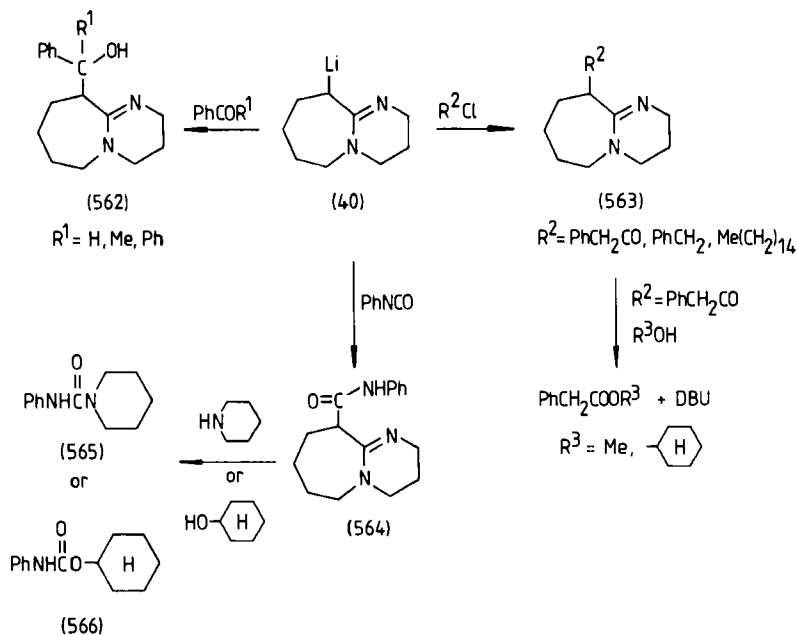
Compound **558** has been characterized via UV, IR, and  $^1\text{H}$ -NMR data (73MI1).

## VIII. Appendix

### A. DIAZABICYCLO[5.4.0]UNDEC-7-ENE (DBU)

#### 1. Reactions of DBU

Lithiated DBU (**40**), prepared from DBU and *n*-butyllithium, was reacted with benzophenone, acetophenone, benzaldehyde, phenylacetyl chloride, benzyl chloride, 1-bromopentadecane and phenyl isocyanate to give the respective 6-substituted pyrimido-[1,2-*a*]azepines (**562–564**) (86JHC885). When heated at 150 or 180°C, the hydroxy derivatives **562** decomposed and the starting ketones and DBU were recovered.



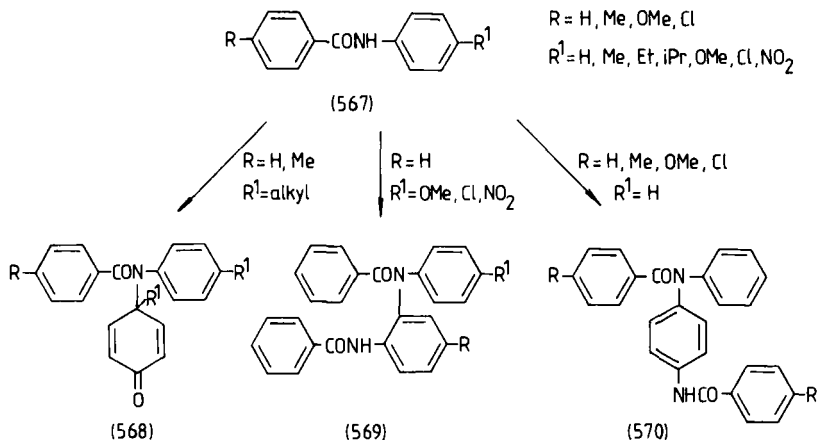
When the 6-phenylacetyl derivative (**563**,  $\text{R}^2 = \text{PhCH}_2\text{CO}$ ) was heated with alcohols, the corresponding esters were obtained in low yields. The reactions of piperidine and cyclohexanol with **564** at  $150^\circ\text{C}$  in dimethylformamide gave urea and urethane derivatives (**565** and **566**) in 25 and 22% yields, respectively. Compound **564** formed a complex with magnesium ion.

Polymer-supported DBU (PDBU) was prepared from DBU and chloromethylated 98:2 styrene-divinylbenzene copolymer (85JAP(K)177006). The PDBU reagent can be used as an esterification catalyst or dehydrohalogenating agent. It can be regenerated quantitatively by treatment with sodium hydroxide in methanol.

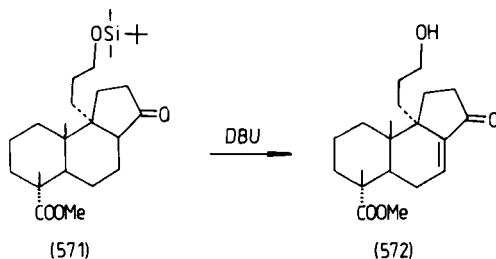
## 2. Applications of DBU in Syntheses

**a. Applications of DBU in Reductions and Oxidations.** The formate salt of DBU was prepared in aqueous isopropanol from DBU, carbon dioxide, and hydrogen under pressure in the presence of rhodium trichloride and triphenylphosphine (85EUP151510).

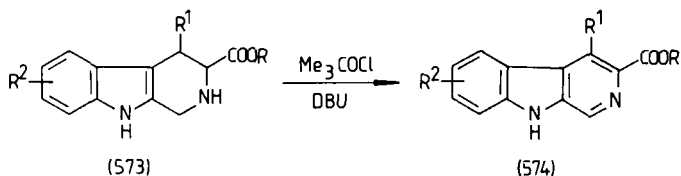
$\text{DBU}\cdot\text{CCl}_4$  and  $\text{DBU}\cdot\text{CBrCl}_3$  proved to be mild oxidation reagents for compounds containing active hydrogens (85MI7). Thus,  $\alpha$ -diketones, disulfides and coumarin were obtained in high yields from  $\alpha$ -ketols, thiols, and 3,4-dihydrocoumarin, respectively, under mild conditions.



Anodic oxidation of 4- and 4'-substituted benzanilides (**567**) was investigated by cyclic voltammetry and controlled potential electrolysis at a glassy carbon electrode in acetonitrile in the presence of DBU or DBU perchlorate (85CPB1407). Depending on the nature of the 4'-substituent, three different types of dimers (**568**–**570**) were obtained.

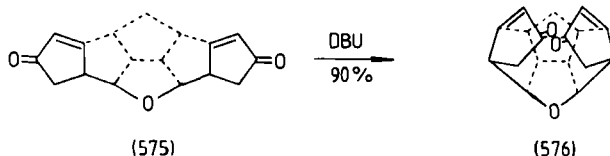


In the total synthesis of (+)-3-deoxyaphidicolin, the silyl enol ether (**571**) was converted with DBU to the  $\alpha,\beta$ -unsaturated ketone (**572**) in 55% yield (85TL2685).

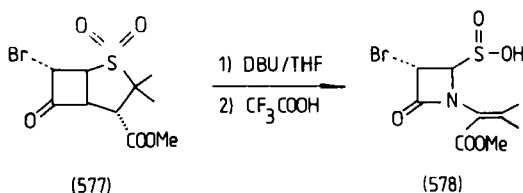


$\beta$ -Carboline-3-carboxylates (**574**) were prepared through the dehydrogenation of 1,2,3,4-tetrahydro- $\beta$ -carboline-3-carboxylates (**573**) with *tert*-butyl hypochlorite in the presence of a tertiary amine (e.g., DBU) in an inert solvent (86GEP3504045).

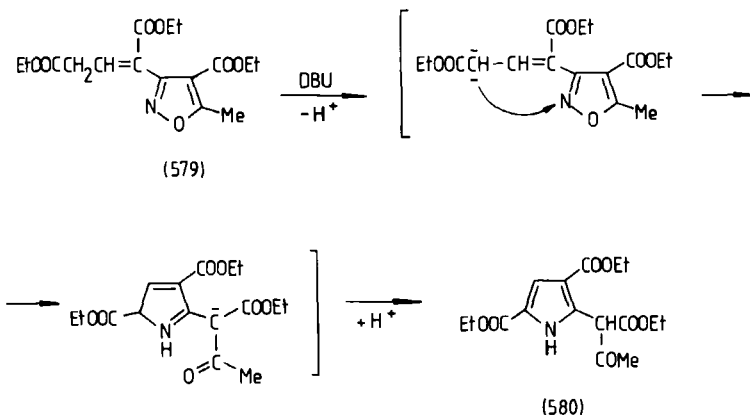
b. *Applications of DBU in Isomerizations and Rearrangements.* The bis enone (**575**) was isomerized smoothly to 8-oxohexacyclooctadecadienedione (**576**) in almost quantitative yield in the presence of a catalytic amount of DBU in refluxing dry dichloromethane (85JA7519).



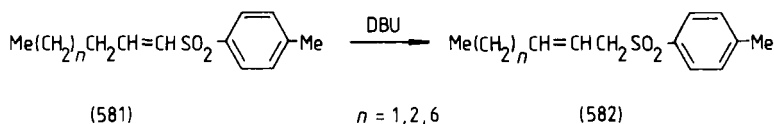
Treatment of 6 $\alpha$ -bromo-1,1-dioxypenicillanate (**577**) with DBU in tetrahydrofuran at 0–5°C for 1 hr gave the sulfenic acid salt (**578**), which was transformed into the free acid by neutralization with trifluoroacetic acid (86JOC399). During the ring-opening reaction the stereochemistry of the sulfenic acid (**578**) was retained (3,4-trans).



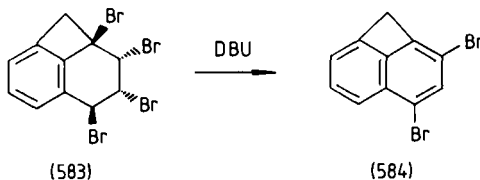
The pyrazole **580** was formed in 42% yield when the oxazole **579** was treated with DBU in ether at ambient temperature (86JCS(P1)927).



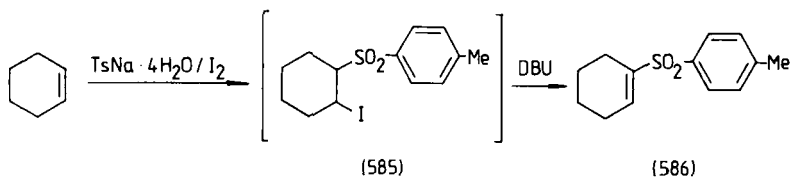
The isomerization of vinylic sulfones **581** to allylic sulfones **582** in high yields was carried out with DBU in acetonitrile (86CL289).



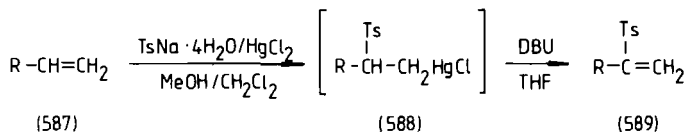
c. *Applications of DBU in Eliminations.* Treatment of tetrabromotetrahydrocyclobuta[*d,e*]naphthalene **583** with DBU in tetrahydrofuran at room temperature gave dibromobuta[*d,e*]naphthalene **584** in 75% yield [85JOC5710].



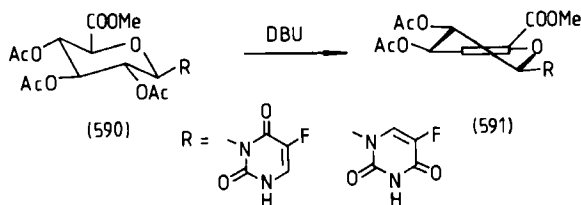
Iodosulfonation of cyclohexene with sodium *p*-toluenesulfinate tetrahydrate and iodine in methanol at ambient temperature, and subsequent dehydroiodination of the product **585** with DBU at room temperature in acetonitrile, afforded 1-tosylcyclohexene (**586**) in 76% yield (86CL289).



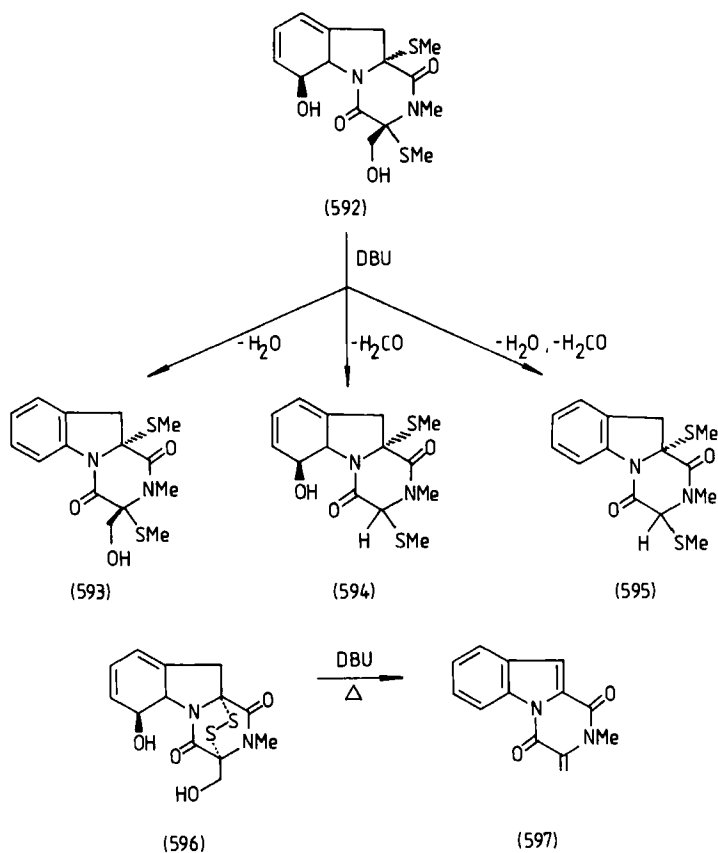
The reaction of 1-alkenes **587** with sodium *p*-toluenesulfinate tetrahydrate and mercury(II) chloride in a mixture of methanol and dichloromethane gave addition products **588**. Treatment of **588** with DBU at room temperature in tetrahydrofuran afforded 2-tosyl-1-alkenes **589** (86CL289).



2,3,4-Tri-*O*-acetyl- $\beta$ -D-glucopyranosyls **590** afforded 4',5'-unsaturated nucleosides **591** on the action of DBU (85MI5).



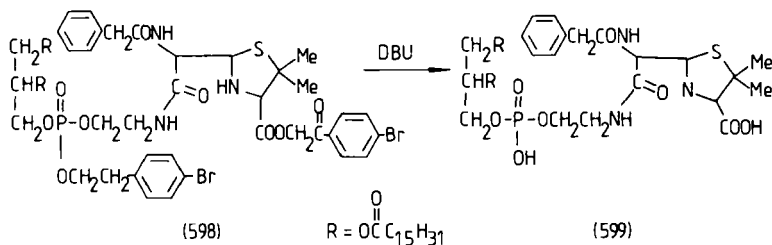
Bisdethiobis(methylthio)gliotoxin **592** was heated in dioxane at 70°C for 2 hr in the presence of DBU, to afford a mixture of compounds **593–595** (86CPB340). Under similar conditions pyrazino[1,2-*a*]indole-1,4(2*H*,3*H*)-dione **597** was obtained from gliotoxin **596**.



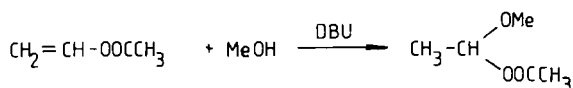
Saturated and unsaturated primary long-chain fatty acids were decarboxylated by heating at 340–360°C in the presence of DBU and copper(I)

bromide (86MI1). The stereochemistry of the unsaturated moiety of the fatty acids was usually retained.

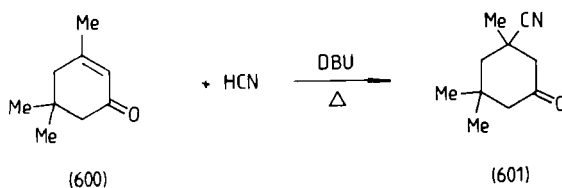
Thiazolidine **598** was deprotected with DBU in chloroform at ambient temperature for 20 hr to give chromatographically pure **599** in 78% yield (86TL271).



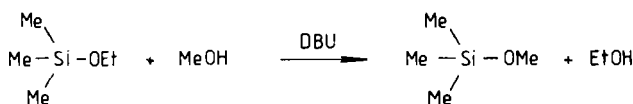
d. *Applications of DBU in Additions.* 1-Methoxyethyl acetate was prepared in 29.7% yield from vinyl acetate and methanol in the presence of DBU (85EUP150106).



Treatment of isophorone **600** with hydrogen cyanide gave 3-cyano-3,5,5-trimethylcyclohexanone **601** in 96.5% yield based on hydrogen cyanide (86JAP(K)33158).



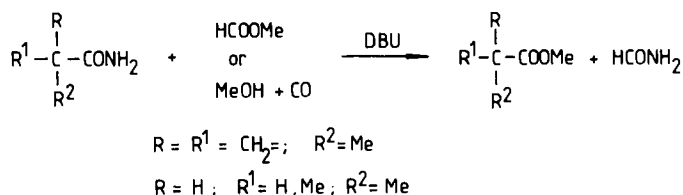
e. *Applications of DBU in Substitutions and Condensations.* Deoxynojirimycin was *N*-alkylated in 67% yield with 1-bromododecane in aqueous acetonitrile in the presence of DBU at 65°C for 7 days (85MI8).



Trimethylethoxysilane was transesterified by methanol in the presence of DBU to give trimethylmethoxysilane in 30.2% conversion (85EUP152241).



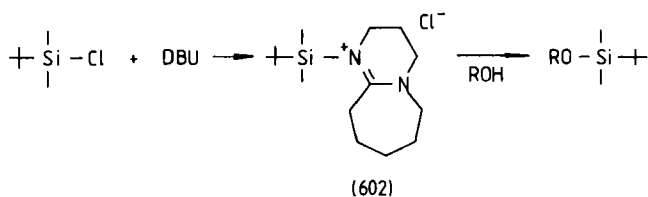
Ethyl *N*-phenylcarbamate was transesterified by methanol in the presence of DBU to afford methyl *N*-phenylcarbamate in 18% conversion (85EUP152240).



Transesterification of ethylene carbonate with methyl acetate in the presence of DBU gave dimethyl carbonate and 1,2-ethanediol acetate in 4% conversion (85EUP150962).

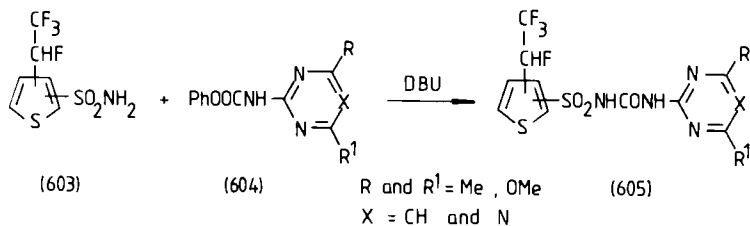
Treatment of carboxamides with methyl formate or methanol and carbon monoxide in the presence of DBU in an autoclave at 180–200°C and 50–200 atm gave a mixture of esters and formamide with high selectivity (85GEP3436608).

Dehydrochlorination of organochlorohydrogermanes in the presence of DBU afforded a mixture of organochloropolygermanes in good yields (85JOMC15).

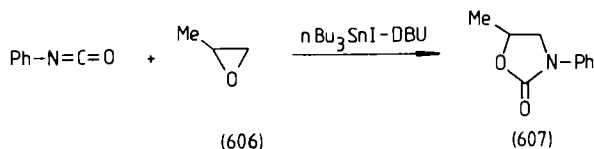


DBU proved to be an effective and selective catalyst for the *tert*-butyldimethylsilylation of primary and secondary alcohols at ambient temperature in different solvents in the presence of DBU (85BCJ3669). It is assumed that DBU forms a complex **602** with *tert*-butyldimethylchlorosilane, which subsequently reacts with alcohols. The *tert*-butyldimethylsilylation of the tertiary hydroxy group did not occur after even a prolonged reaction time. When 2-ethyl-1,3-hexanediol, 1,3-butanediol, and 1-phenyl-1,2-ethanediol were reacted, the corresponding primary silyl ether was obtained almost exclusively.

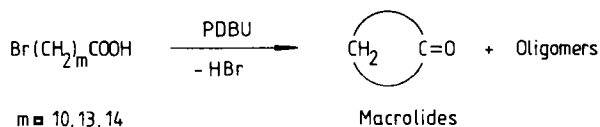
Thiophenesulfonamide derivatives **605** were obtained in the reaction of thiophenesulfonamides **603** with phenyl carbamates **604** in the presence of DBU in acetonitrile at ambient temperature (86JAP(K)152680).



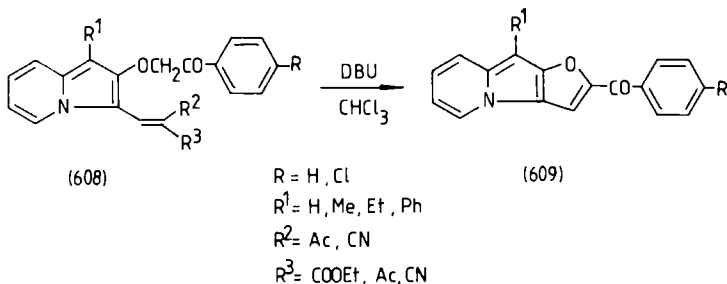
f. *Applications of DBU in Cyclizations and Cyclocondensations.* The cycloaddition of phenyl isocyanate with propylene oxide **606** gave oxazolinone **607** only in trace amount when tri-*n*-butyltin iodide was applied as catalyst. However, compound **607** was formed in 41% yield when an organotin halide-DBU complex generated *in situ* was used [86JOC2177].



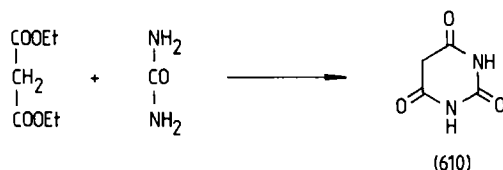
The intra- and intermolecular reactions of  $\omega$ -bromocarboxylic acids in the presence of PDBUs in toluene afforded mainly macrolides with small amounts of linear oligomers (85MI9).



On the action of DBU in chloroform 2-aryl-methoxy-3-vinylindolizines **608** afforded 2-aryl-furo[2,3-*b*]indolizines **609** in 40–90% yields (85MI4).



Barbituric acid (**610**) was obtained in 20–25% yields in the reaction of diethyl malonate and urea in the presence of DBU in refluxing alcohols (86EUP178917).



### 3. Applications of DBU in the Synthesis of Macromolecules

DBU and its salts have been applied as catalysts or components of catalysts for the cross-linking of heat-resistant siloxane coatings (85JAP(K)199056), of epoxy resin adhesives for printed circuit boards (85JAP(K)186579), and of epoxy resin coatings for photoelectric converters (85JAP(K)206078), and for the polymerization of tetramethylxylylene isocyanate with aliphatic polyols (85EUP154180), and of active hydrogen compounds with polyacrylates (85GEP3508399). DBU and its salts were used in the preparation of the following materials: epoxy resin compositions (86JAP(K)12724; 86JAP(K)62512; 86JAP(K)62514), for semiconductor sealing (86JAP(K)89221), or providing transparent hardened objects (86JAP(K)31424); thermosetting aliphatic polycarbonates (86GEP3501246); fluoroelastomer compositions (86JAP(K)12741); vulcanizable halogen-containing polymer compositions (86JAP(K)78875); silver halide photographic emulsion (86JAP(K)11736); chlorine bleach-compatible liquid detergent compositions (86USP4594184); organic solvent-soluble polyimide compound (86JAP(K)111317); and an electrically conductive coating composition of a chlorosulfonated polyethylene (86USP4578286). DBU was applied for the surface treatment of vulcanized fluoro rubbers to reduce the surface tack and friction (86JAP(K)81437).

DBU salts were utilized as vulcanization accelerators for elastomer curing compositions (85JAP(K)235864). DBU was patented as a stabilizer for polyisocyanates and isocyanates (85GEP3403500). DBU was applied in the manufacturing of optical recording disks (85EUP144705) and photosensitive resin plates (85JAP(K)98433).

### 4. Miscellaneous

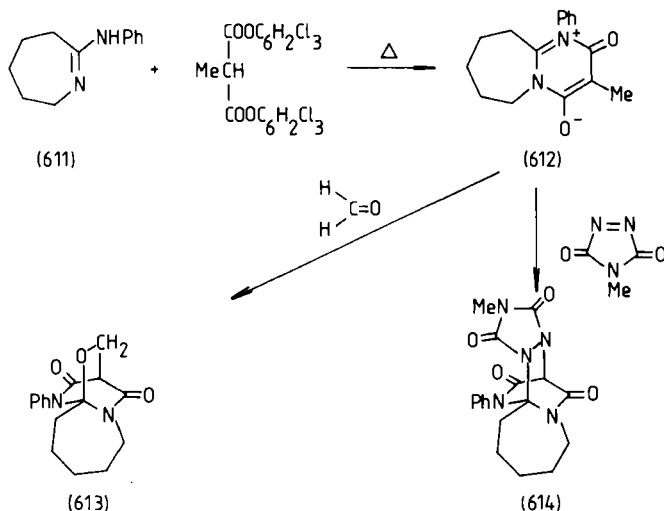
Polyanionic polysaccharides were solubilized through the use of DBU (85EUP161188).

Kinetic studies of the deprotonation of  $\{H \text{ and } DMO(CO)_2[1,2\text{-bis(diphenylphosphino)ethane}]_2\}$  tetrafluoroborate  $[HMo(CO)_2dppe_2^+]$  and  $DMo(CO)_2dppe_2^+$ ,  $\{HMo(CO)_2 1,2\text{-bis(dimethylphosphino)ethane}\}_2\}$  tetrafluoroborate, and  $\{HMo(CO)_2[1,2\text{-bis(diethylphosphino)-ethane}]_2\}$  tetrafluoroborate were carried out in the presence of different bases (86IC2894). When DBU was applied, as a bulky and strong base, a large kinetic isotope effect was observed for the deprotonation of  $HMo(CO)_2dppe_2$  versus  $DMo(CO)_2dppe_2$ :  $k_H/k_D = 3.0$ . This value indicated that the deprotonation reactions involve substantial bond cleavage in the transition state in the presence of DBU.

## B. FURTHER PYRIMIDO[1,2-*a*]AZEPINES

### 1. Synthesis

By the reaction of bis(2,4,6-trichlorophenyl)-methylmalonate with 2-phenylamino-4, 5, 6, 7-tetrahydro-3*H*-azepine (**611**) at 160°C for 20 min, the 1-phenylpyrimidoazepine **612** was prepared in 81% yield (85CB4567).



### 2. Reactions

1-Phenylpyrimidoazepine **612** readily undergoes 1,4-dipolar cycloaddition reactions (85Ag604, 85CB4567). The reaction of compound **612** and formaldehyde resulted in the formation of tricyclic compound **613** in a regiospecific

manner (85Ag604). Mesomeric betaine **612** and 4-methyl-1,2,4-triazoline-3,5-dione gave tetracyclic derivative **614** in 87% yield (85CB4567).

### 3. Physicochemical Properties

The structure of mesomeric betaine **612** was characterized via IR,  $^1\text{H}$  NMR and MS data (85CB4567).

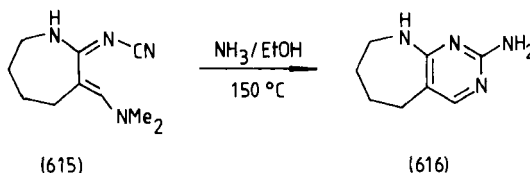
### 4. Applications

Perhydropyrimido[1,2-*a*]azepine was applied as a hardening catalyst in the preparation of liquid crystal displays with molecular orientation-controlling films (85JAP(K)258517).

## C. PYRIMIDO[4,5-*b*]AZEPINES

### 1. Synthesis

2-Aminopyrimido[4,5-*b*]azepine **616** was obtained in 41% yield in the reaction of azepine **615** and alcoholic ammonia in a bomb at 150°C (85MI6).



## References

- |              |  |
|--------------|--|
| 59LA166      | S. Petersen and E. Tietze, <i>Justus Liebigs Ann. Chem.</i> <b>623</b> , 166 (1959).   |
| 61GEP1082268 | E. Tietze and S. Petersen, German Patent 1,082,268 [ <i>CA</i> <b>55</b> , 15522 (1961)].  |
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# Claisen Rearrangements in Heteroaromatic Systems

CHRISTOPHER J. MOODY

*Department of Chemistry,  
Imperial College of Science and Technology,  
London SW7 2AY, England*

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## I. Introduction

In the 75 years since its discovery (12CB3157), the Claisen rearrangement has been widely studied. However, it is during the last 20 years that the reaction has come of age, particularly with respect to its use in organic synthesis, with the discovery of new reagents such as amide acetals and new experimental conditions such as the ester enolate rearrangement. It is now recognized that the Claisen rearrangement falls within the general class of [3,3]-sigmatropic reactions, and as such it is closely related to other processes such as the Cope rearrangement. The Claisen rearrangement continues to hold the interest of synthetic and mechanistic chemists alike, and therefore has already been the subject of several reviews (68QR391; 75OR1; 77ACR227;

77S589; 80T2; 84CRV205) covering all aspects of the reaction. This article is concerned with Claisen rearrangements in heteroaromatic systems (69M11), and is effectively an update of an earlier article that appeared in Volume 8 of this series (67AHC(8)143).

## SCOPE AND ORGANIZATION

This article will concentrate on the thermal rearrangement of heteroaryl allyl ethers and their thioether analogues (1), which in some ring systems are more common than their oxygen counterparts. Rearrangements in which the heteroaromatic ring forms part of the allyl system (2) are also covered, as are [3,3]-rearrangements of *N*-allyl five-membered heteroaromatic compounds, for example *N*-allylindoles, even though they are not strictly Claisen rearrangements. Rearrangements of reduced heterocyclic compounds such as the *N*-allyltetrahydroquinoline (3) (83CPB2220; 86CC1308), however, are excluded since these are considered to be examples of amino-Claisen rearrangements of aniline derivatives.



(1)



(2)



(3)

(Het = heteroaromatic ring; X = O or S)

The actual synthesis of the substrates for Claisen rearrangements in heteroaromatic systems is beyond the scope of this article, since the preparation of heteroaryl allyl ethers and their sulfur analogues is not always straightforward. Problems of allylation on nitrogen rather than oxygen (or sulfur) and of rearrangement occurring under the conditions of the alkylation reaction are common, although in some cases the ethers may be prepared by nucleophilic displacement of heteroaryl halides. Provided that the heteroaryl allyl ethers and thioethers are isolable, the Claisen rearrangement occurs on heating, either neat or in a solvent, and just as for other systems, the use of high-boiling solvents such as *N,N*-dimethylaniline (DMA), quinoline, or decalin is common (75OR1). The addition of acetic (or other) anhydride to the solvent is also quite common, and serves to trap the initial product of Claisen rearrangement, the heterocyclic OH or SH compound that is likely to be unstable, by *in situ* acylation.

This article is organized by ring system. Thus, Claisen rearrangements in five-membered heterocyclic rings are covered in Section II, rearrangements of *N*-allyl heterocycles in Section III, and Claisen rearrangements of six-

membered heteroaromatic compounds in Section IV. Claisen rearrangements in the benzene ring of benzo-fused systems are dealt with separately because they raise the important topic of the regioselectivity of the rearrangement. No attempt has been made to include comprehensive tables covering all known Claisen rearrangements in heterocyclic systems. The literature has been covered since 1967, the date of the previous review in this series, although important pre-1967 work is included where relevant.

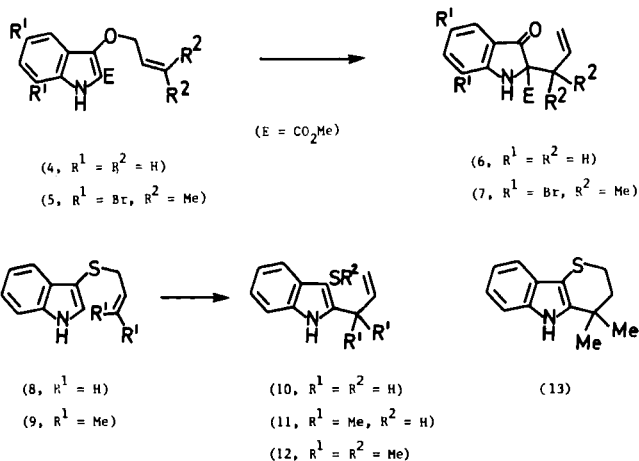
## II. Claisen Rearrangements in Five-Membered Heteroaromatic Rings

### A. PYRROLES AND INDOLES

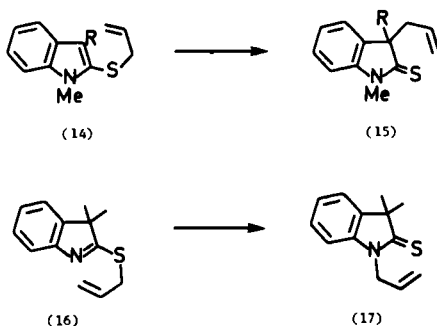
Simple Claisen rearrangements of pyrrol allyl ethers or thioethers are rare because of the inaccessibility of the O- or S-substituted rings. 2-(Allylthio)pyrrole rearranges on heating in a mixture of quinoline and acetic anhydride to give 2-(acetylthio)-3-allylpyrrole in 71% yield (78CJC221), illustrating the use of acetic anhydride to intercept the initially unstable Claisen rearrangement product, a mercaptopyrrole. Similarly, 2,5-bis(allylthio)pyrrole rearranges to 2,5-bis(acetylthio)-3,4-diallylpyrrole.

In the indole series, Claisen rearrangements, especially the thio-Claisen rearrangement, are more common. The 3-allyloxyindoles **4** and **5**, obtained by *O*-alkylation of the 3-indolinone under appropriate conditions, rearrange readily on heating in cyclohexane, or on standing in contact with silica gel, to give the 3-indolinones **6** and **7** (71CB1863). The inversion of the 3,3-dimethylallyl group confirms the [3,3]-sigmatropic nature of the reaction, and also constitutes a useful method for the introduction of this five-carbon unit into the indole 2-position. The alkaloid echinulin contains such a 2-isoprenyl group. 3-(Allylthio)indole **8** rearranges on heating to 150°C to give the 2-allylindole **10** (51%), although in the case of the *S*-(3,3-dimethylallyl) derivative (**9**), the initial rearrangement product (**11**) is accompanied by the cyclized compound **13** (74CB3915). The formation of sulfur-containing rings in the thio-Claisen rearrangement is well known (75OR1). The thio-Claisen rearrangement in indoles can also be induced by *S*-alkylation of the thioether. Thus treatment of the indole **9** with methyl fluorosulfonate and potassium carbonate in benzene at room temperature results in formation and spontaneous rearrangement of the *S*-methylsulfonium salt to give the indole **12** (53%) (74CB3915).

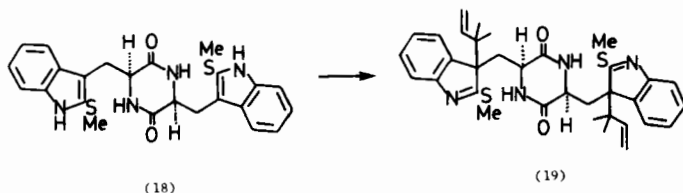
In the corresponding 2-*S*-allylindoles, rearrangement occurs as expected to give 3-allyl-2-thioxindole derivatives even when the 3-position is already



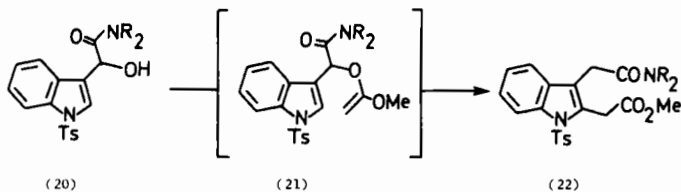
substituted. Thus the indoles **14** ( $R = \text{H}$  or  $\text{Me}$ ) rearrange on heating in toluene to the thioxindoles **15**, and 1,3-dimethyl-2-(propargylthio)indole gives the corresponding 3-allenyl derivative. When the 3-position is blocked as in the indolenine **16**, the allyl group migrates to nitrogen to give the thioxindole **17** on heating in tetralin (70CC168).



Again the rearrangement can be induced by *S*-methylation, 1-methyl-2-(3,3-dimethylallylthio)indole being converted into 1-methyl-3-(1,1-dimethylallyl)-2-(methylthio)indole on treatment with methyl fluorosulfonate under mild conditions. The same indole product results from treatment of 1-methyl-2-(methylthio)indole with 3,3-dimethylallyl bromide, and the possible role of such rearrangements induced by biological prenylation in the biosynthesis of indole alkaloids has been discussed (70CC967). Along these lines, a biomimetic synthesis of the alkaloid amaumomine relies on a thio-Claisen rearrangement as a key step (85TL847). Reaction of the indole **18** with 3,3-dimethylallyl bromide and potassium carbonate in dioxane at room temperature gives the key intermediate **19** containing the isoprenyl group.

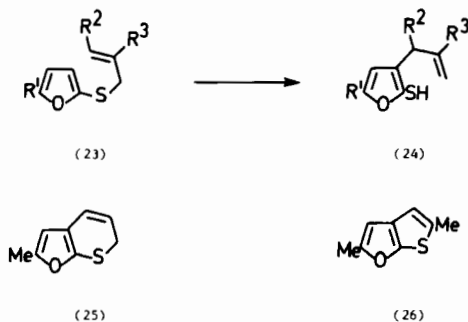


Claisen rearrangements of indole derivatives also feature in other alkaloid syntheses, although in these cases the indole 2,3-bond forms part of the *allyl* systems in the [3,3]-process. For example, reaction of the 3-substituted indole **20** (Ts = *p*-toluenesulfonyl) with triethyl orthoacetate gives the 2,3-disubstituted indole **22** via rearrangement of the intermediate ketene acetal (**21**) (86JOC123). Other similar rearrangements have been reported, and elegantly used in the synthesis of indole alkaloids by Raucher and coworkers (78JA4902; 79TL3057; 80TL4335; 81JA2419; 83T3731).



## B. FURANS, THIOPHENES, AND THEIR BENZO DERIVATIVES

Most of the Claisen rearrangements in furans and thiophenes are thio-Claisen rearrangements, and most are in thiophenes rather than furans. In the furan series, the 2-(allylthio) derivatives **23** undergo Claisen rearrangement on heating to give the expected product (**24**) in varying yield (79ZOK1970; 82DOK(267)97). On further heating, the initial product (**24**,  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ,  $R^3 = \text{Br}$ ) cyclized to the furothiapyran **25** and the furothiophene **26** with loss of HBr.

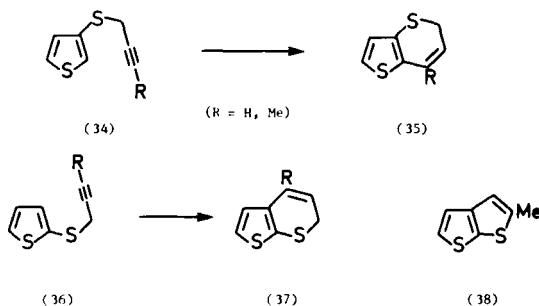






In contrast with the above work, a group in Russia has investigated the thio-Claisen rearrangement of a range of 2-(allylthio)thiophenes, and in most cases isolated the 2-mercaptothiophene product (82DOK(267)97; 82KGS181; 82KGS1195; 83KGS1348).

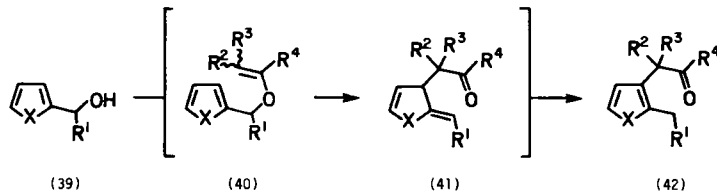
S-Propargylthiophenes also undergo Claisen rearrangement (69RTC732; 70RTC110; 72RTC785). Thus, the 3-propargylthio derivatives **34** ( $R = H$  or Me) give high yields of the thienothiapyrans **35**, formed by cyclization of the initial rearrangement product, on heating in hexamethylphosphoramide (HMPA). The products formed from the isomeric propargyl compounds **36** are solvent dependent. In HMPA the thienothiapyran **37** ( $R = H$  or Me) is formed in high yield, but in the presence of an amine the initial product of Claisen rearrangement cyclizes to give the thienothiapyran (**37**,  $R = H$ ) in competition with the thienothiophene (**38**), the latter being the major product.



2-(Allylthio)benzo[*b*]thiophenes and benzofurans undergo Claisen rearrangement to give the corresponding 3-allyl-2-mercapto derivatives, the rearrangement occurring even at room temperature over prolonged periods (81KGS615; 82KGS1338).

Intermediates of type **40**, which can be generated from furfuryl alcohol or the thiophene analogue (**39**) by various reagents, undergo Claisen rearrangement (Table I). Thus reaction of furfuryl alcohol with ynamines gives the furans **42a**, and in the case of the reaction with  $\text{MeC}\equiv\text{CNEt}_2$  the initial product of rearrangement, the nonaromatic furan (**41a**,  $R^2 = \text{Me}$ ), can be isolated. The furan **42b** is only a minor product since the initial rearranged compound (**41b**) undergoes a further [3,3]-rearrangement involving the vinyl group to give 2-(4-formylpent-4-enyl)furan in competition with direct aromatization to give **42b**. In the reaction of the furan, thiophene, and *N*-tosylpyrrole derivatives with orthoesters, the 2,3-disubstituted products (**42c**, **42d**, **42e**) are formed in varying yields, with the yield of pyrrole being the lowest. The ester enolate Claisen rearrangement occurs readily when the furan and the thiophene derivatives obtained by acylation of the alcohols **39f** and **39g** are

TABLE I  
CLAISEN REARRANGEMENTS IN DERIVATIVES OF FURFURYL ALCOHOL ANALOGUES



	X	R <sup>1</sup>	Reagents	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	Reference
<b>a</b>	O	H	R <sup>2</sup> C≡CNEt <sub>2</sub> , C <sub>6</sub> H <sub>6</sub> , heat	Me or Ph	H	NEt <sub>2</sub>	<i>a</i>
<b>b</b>	O	H	H <sub>2</sub> C=CHCMe=CHOEt, Hg(OAc) <sub>2</sub>	Me	CH=CH <sub>2</sub>	H	<i>b</i>
<b>c</b>	O	CO <sub>2</sub> Et					
<b>d</b>	S	CO <sub>2</sub> Et	R <sup>2</sup> CH <sub>2</sub> C(OEt) <sub>3</sub>	H, Me, or Pr	H	OEt	<i>c</i>
<b>e</b>	NTs	CO <sub>2</sub> Et					
<b>f</b>	O	H	R <sup>2</sup> CH <sub>2</sub> COCl, then LDA, TMSCl <sup>d</sup>	H or Me	H	OSiMe <sub>3</sub>	<i>e</i>
<b>g</b>	S	H	R <sup>2</sup> CH <sub>2</sub> COCl, then LDA	R <sup>2</sup>	H	OLi	<i>f</i>

<sup>a</sup> 69CR(C)1446.

<sup>b</sup> 70JCS(C)220.

<sup>c</sup> 79JOC1885.

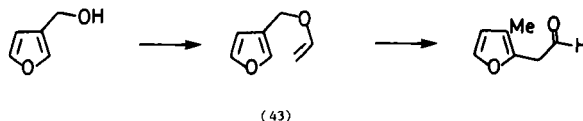
<sup>d</sup> LDA, lithium diisopropylamide; TMSCl, trimethylsilyl chloride.

<sup>e</sup> 85H(23)549.

<sup>f</sup> 83BCJ1665.

treated with base. In both cases the final product after aqueous work-up is the carboxylic acid corresponding to **42f** and **42g**.

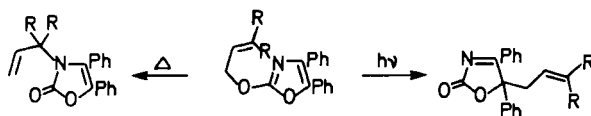
The corresponding rearrangement of substrates derived from furan-3-methanol is much more sluggish (70JCS(C)220). The intermediate vinyl ethers, for example **43**, are easily isolated, and require a temperature of 160°C for rearrangement to occur (74JIC900).



### C. AZOLES AND BENZAZOLES

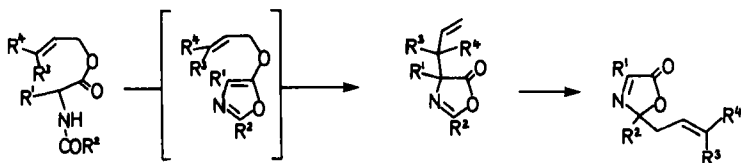
3-Allyloxy-1-phenylpyrazole undergoes Claisen rearrangement on heating to about 250°C to give 4-allyl-3-hydroxy-1-phenylpyrazole as the major (50%) product (66JOC1538). Under slightly different conditions some [3,3]-rearrangement to nitrogen occurs to give 2-allyl-1-phenylpyrazol-3-one as a minor product (67JOC2956). The *N*-allylpyrazolone rearranges to the 4-allyl-3-hydroxy compound in low yield on strong heating. Reaction of ethyl 5-hydroxy-1-phenylpyrazole-3-carboxylate with allyl bromide and potassium carbonate in refluxing benzene leads directly to ethyl 4,4-diallyl-5-oxo-1-phenylpyrazole-3-carboxylate (72%), presumably via a double Claisen rearrangement (81YZ271). 3-Allyloxy-4,5-dihydro-5-phenylisoxazole undergoes Claisen rearrangement on heating in DMA for 15 min to give the *N*-allyl-isoxazolinone (77%) (83JOC1796).

Several Claisen rearrangements have been reported in the oxazole series. 2-Allyloxy-4,5-diphenyloxazoles rearrange in high yield on heating to 155°C to give 3-allyloxazolones, the 3,3-dimethylallyl group migrating with inversion thus confirming the [3,3]-sigmatropic nature of the rearrangement (82TL915; 84JOC399). The corresponding propargyloxyoxazole gives the *N*-allenyloxazolone. On irradiation, however, the allyl group migrates to C-5, and in the case of the 3,3-dimethylallyl group the major product does not have the group inverted (Scheme 1); a radical dissociation-recombination mechanism is suspected. 2-Allyloxythiazole is also reported to undergo Claisen rearrangement at 140°C to give 3-allylthiazol-2-one (73MI2), although in poor yield.



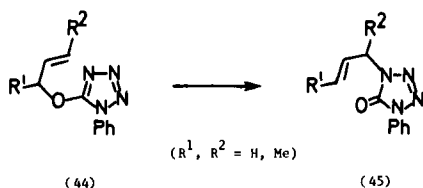
SCHEME 1

A series of papers by Steglich and co-workers describes the Claisen rearrangement of 5-allyloxazoles. These are prepared by cyclodehydration of *N*-acyl amino acid allyl esters with phosgene (75AG(E)58; 77AG(E)394). The allyloxazoles are not isolated, rearranging under the reaction conditions to the corresponding 4-substituted oxazolones, which themselves rearrange by a further [3,3]-aza-Cope rearrangement on heating (Scheme 2). If the allyl chain contains a chiral center then the double [3,3]-rearrangement sequence can be used as a method of chirality transfer (86T2063). Alternatively, the initial rearrangement product can be hydrolyzed to an amino acid derivative (82JOC3933).



SCHEME 2

Finally, in the series of monocyclic azoles, 5-allyloxytetrazoles **44** undergo Claisen rearrangement on heating to 100–150°C to give the expected tetrazolones **45** (67JOC2956).



A number of Claisen rearrangements of 2-allyloxy- or 2-allylthiobenzimidazoles (67AHC(8)143) and -benzothiazoles have been reported. These are summarized in Table II. In some cases the deuterium isotope effects have been studied, and these confirm the concerted nature of the rearrangement (73MI1; 73MI2). The 2-(propargylthio)benzimidazole **46** rearranges as expected, although the initial product cyclizes to give the thiazolobenzimidazole **47** (74TL2643).

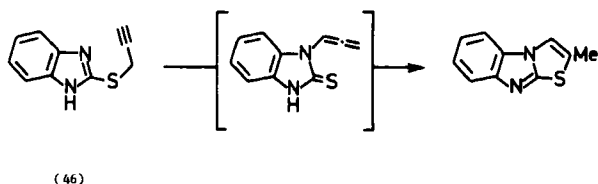
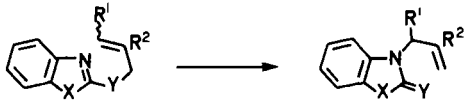


TABLE II  
CLAISEN REARRANGEMENTS OF 2-ALLYLOXY- AND  
2-ALLYLTHIOBENZIMIDAZOLES AND -BENZOTHAZOLES

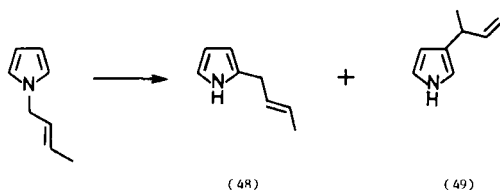


X	Y	R <sup>1</sup>	R <sup>2</sup>	Reference
NH	S	H	H	<i>a</i>
NMe	O or S	H	H	<i>b, c, d</i>
NMe	O or S	Me	H	<i>b, c, d</i>
NH	S	H	CO <sub>2</sub> H	<i>e</i>
O or S	O	H	H	<i>f</i>
O or S	S	H	H	<i>d</i>
S	O	Ph or H	H	<i>g</i>

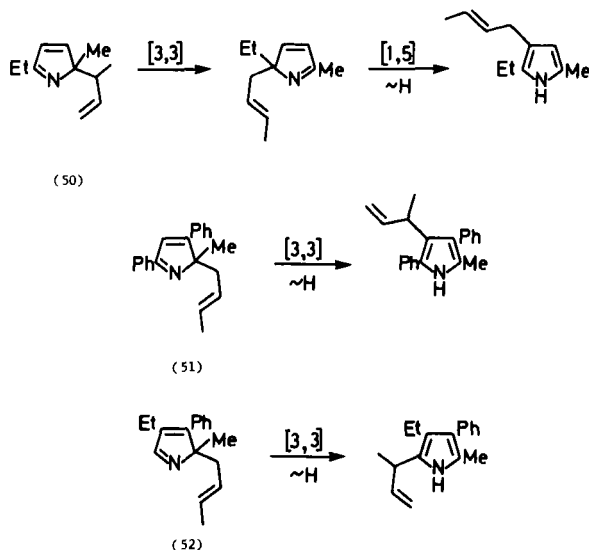
<sup>a</sup> 83JHC813.<sup>b</sup> 68ZOR1114.<sup>c</sup> 68MI1.<sup>d</sup> 73MI1.<sup>e</sup> 84H(22)1049.<sup>f</sup> 67JOC2956.<sup>g</sup> 73MI2.

### III. Rearrangement of *N*-Allyl Five-Membered Heteroaromatic Rings

[3,3]-Sigmatropic rearrangements of *N*-allyl five-membered heterocyclic compounds are more correctly considered as aza-Cope rearrangements rather than Claisen rearrangements, but are included in this article for completeness. Most of the work has been in the indole series, possibly fueled by speculation that the isoprenylation of tryptophan at C-4 might proceed by rearrangement from N-1 to C-3 and on to C-4 by two successive [3,3]-processes (76T873). The rearrangement of *N*-allylpyrroles has also been studied; thus *N*-crotylpyrrole rearranges on heating to give 2-crotylpyrrole (**48**) and 3-(1-methylallyl)pyrrole (**49**) by competing [1,5]- and [3,3]-sigmatropic shifts, followed in both cases by aromatizing hydrogen shifts (72JA2487).



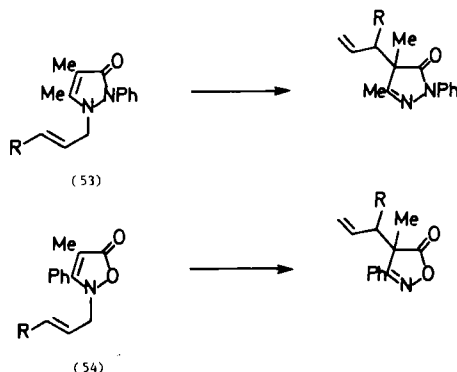
In the related rearrangement of 2-allyl-2*H*-pyrroles, the situation is more complex, and the exact nature of the major process is highly substituent dependent. NMR studies on the rearrangement of the methylallyl-2*H*-pyrrole **50** show that rearrangement proceeds by a [3,3]-process, followed by a [1,5]-shift and a subsequent hydrogen shift (Scheme 3) (75JA360), although closely related 2-crotyl-2*H*-pyrroles rearrange by a [1,5]-sigmatropic shift. Rearrangement of the 2*H*-pyrrole **51** is thought to proceed via a [3,3]-process followed by a hydrogen shift (79TL107), in contrast to the rearrangement of **50**. The effect of substituents at the 3- and 4-positions on the outcome of the rearrangement has been studied. The 3,4-disubstituted 2*H*-pyrrole **52** rearranges by a [3,3]-process (Scheme 3), but in 3,4-unsubstituted 2*H*-pyrroles, the [1,5]-shift predominates (82TL655). Many of these rearrangements, together with their photochemical counterparts, are covered in a recent review on 2*H*-pyrroles (82AHC(32)233).



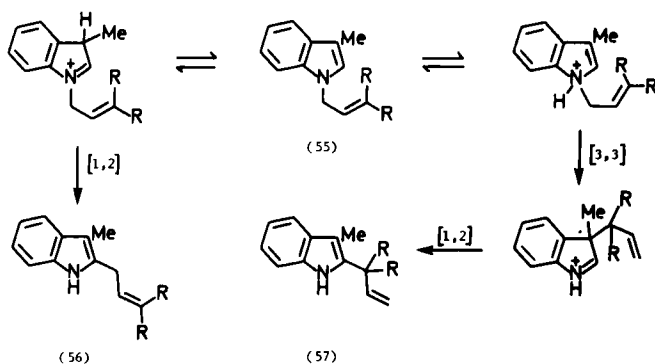
SCHEME 3

*N*-Allylpyrazolones **53** (R = H or Me) and -isoxazolones **54** (R = H or Me) rearrange on heating at 180°C to give the products of the [3,3]-sigmatropic shift in good yield (66TL6413; 69TL543).

Flash vacuum pyrolysis (FVP) of *N*-crotylindole at 450–470°C causes [3,3]-rearrangement to give 3-(1-methylallyl)indole, although this compound readily reverts to starting material and undergoes a [1,2]-shift to 2-(1-methylallyl)indole on heating in a condensed phase (74JOC486). The rearrangement of *N*-allyl heterocycles can often be catalyzed, and refluxing a



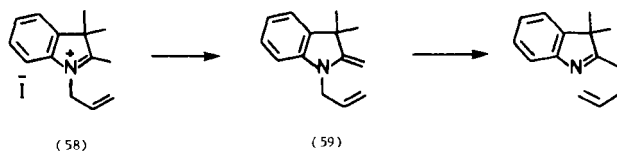
benzene solution of *N*-allylindole in the presence of aluminum chloride gives an 85% yield of 3-allylindole (76BCJ833). The trifluoroacetic acid (TFA) mediated rearrangement of a series of *N*-allylindoles (55) has been studied in detail (74JCS(P1)754), and gives both normal and inverted 2-allylindoles (56 and 57). One interpretation (79MI1) is that the reaction proceeds by competing [3,3]- and [1,2]-shifts in the protonated starting material, the initial product of [3,3]-rearrangement, the 3-substituted indole, rearranging by further [1,2]-shift (Scheme 4), although the intermediacy of an *N*-protonated indole must be highly questionable. However, when 1-(3,3-dimethylallyl)indole-3-carbaldehyde was treated with TFA no rearrangement occurred; instead an interesting cyclization of the prenyl group to the indole 7-position took place (81H(15)713).



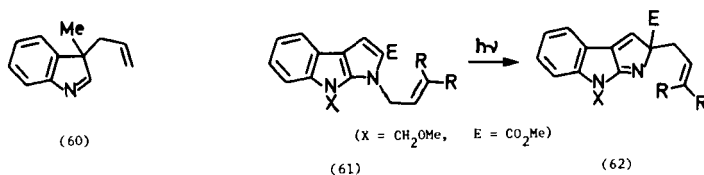
SCHEME 4

The *N*-allylindole derivative 59, prepared by reaction of the iodide 58 with hydroxide, underwent [3,3]-rearrangement on heating to 200°C to give the expected product (68TL5059).





Although not directly relevant to this article, the rearrangement of *N*-allylindole derivatives can also be induced by light. Thus, irradiation of 1-allyl-3-methylindole gives the indolenine (60), which on heating to 250°C reverts to the starting indole (70TH1). Irradiation of 1-(3,3-dimethylallyl)indole gives 3-(3,3-dimethylallyl)indole, and the fact that no allylic inversion occurred suggests that the rearrangement proceeds via a photochemical [1,3]-shift, or possibly via a homolysis–recombination pathway (73TL2451). Similarly, no allylic inversion is observed in the photochemical rearrangement of the related *N*-allylpyrroloindoles 61 to the 2*H*-pyrroloindoles 62 (84JCS(P1)2903).



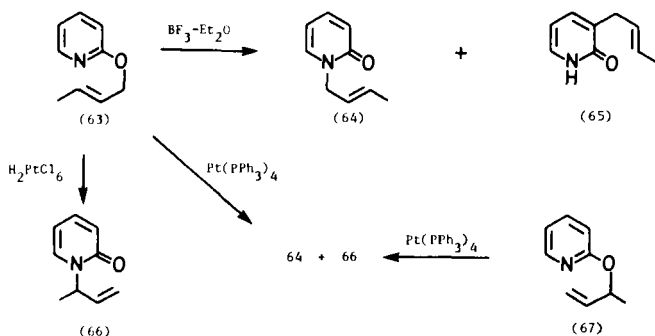
#### IV. Claisen Rearrangements in Six-Membered Heteroaromatic Rings

##### A. PYRIDINES, QUINOLINES, AND ISOQUINOLINES

Although the Claisen rearrangement of 2-allyloxypyridines usually requires high temperatures and often proceeds in poor yield (67AHC(8)143), 2-allyloxy-3,4,5,6-tetrachloropyridine rearranging to the corresponding *N*-allylpyridone (34%) at 184°C, for example (79JCS(P1)2756), the reaction can be catalyzed by transition metal salts or Lewis acids. Thus, heating 2-allyloxypyridine at 90°C in the presence of H<sub>2</sub>PtCl<sub>6</sub> or boron trifluoride–diethyl ether results in a good yield of the Claisen rearrangement product 1-allyl-2-pyridone.

When 2-crotyloxypyridine (63) was heated under similar conditions, however, the results were catalyst dependent (Scheme 5). With boron trifluoride–diethyl ether as catalyst, an 82:18 mixture of the pyridones 64 and 65 was obtained, whereas the H<sub>2</sub>PtCl<sub>6</sub>-catalyzed reaction gave a [3,3]-rearrangement product, the pyridone 66 (68JOC4560). Interestingly, when Pt(PPh<sub>3</sub>)<sub>4</sub> was used as catalyst, 63 and 2-(1-methylallyloxy)pyridine (67) both gave the same 14:86 mixture of the pyridones 64 and 66, suggest-

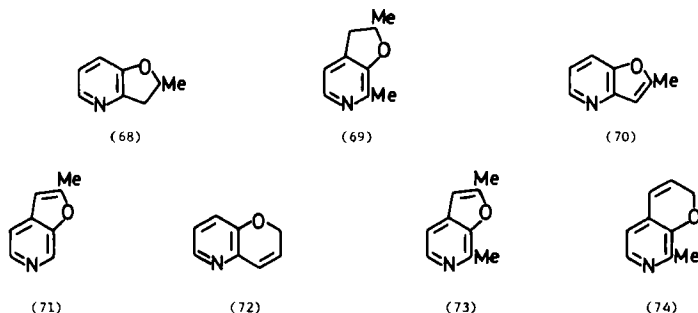
ing that in this case the rearrangement proceeds via a pyridone anion- $\pi$ -allylplatinum cation ion pair mechanism (79TL3949). Indeed in the presence of pentane-2,5-dione, an enolizable  $\beta$ -diketone and a good trap for  $\pi$ -allyl complexes, the products were  $\text{MeCH}=\text{CHCH}_2\text{CH}(\text{Ac})_2$  and 2-pyridone itself.



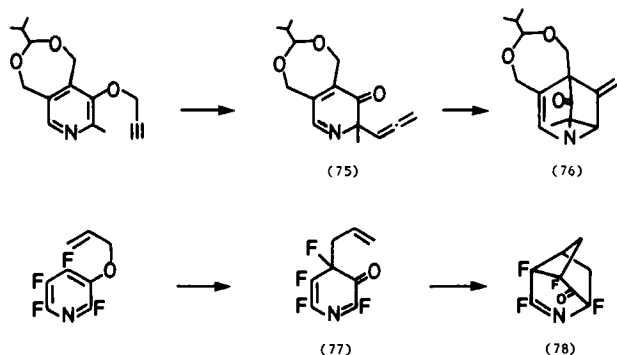
SCHEME 5

The Claisen rearrangement of 2-allylthiopyridine to 1-allyl-2-pyridinethione is also catalyzed by transition metals. The role of the catalyst,  $\text{PdCl}_2(\text{PhCN})_2$ , is particularly important in this case since the reaction is thermodynamically unfavorable, and presumably the product is stabilized by complex formation. When the product is freed from the metal by addition of excess pyridine, it readily reverts to starting material on heating (80JOC5221).

The Claisen rearrangement of 3-hydroxypyridine derivatives can in principle proceed to C-2 and/or C-4. However, in practice the rearrangement of such compounds exhibits some degree of regioselectivity. Thus 3-allyloxypyridine on heating to  $203^\circ\text{C}$  in decane or dimethylformamide (DMF) gives a 70% yield of the dihydrofuro[*b*]pyridine **68**, formed by Claisen rearrangement to the 2-position followed by cyclization, with no evidence for the isomeric furo[*c*]pyridine. When the 2-position is blocked by a methyl group, rearrangement does proceed to the 4-position but in poor yield, 3-allyloxy-2-methylpyridine giving furopyridine **69** (15%). A similar pattern is followed in the corresponding 3-propargyloxypyridines. Heating 3-propargyloxypyridine in DMF gives the furo[*b*]pyridine **70** as the major product together with the isomer **71**. In decane the rearrangement is more regioselective, with the furopyridine **70** and the alternative cyclization product, the pyranopyridine **72**, accounting for over 80% of the rearrangement products. Heating 2-methyl-3-propargyloxypyridine, in which rearrangement to the 2-position is blocked, in DMF gives a low yield (37%) of the furo[*c*]pyridine **73**; in decane the alternative pyranopyridine **74** is formed as the major (22%) product in addition to **73** (11%) (78HCA2542).

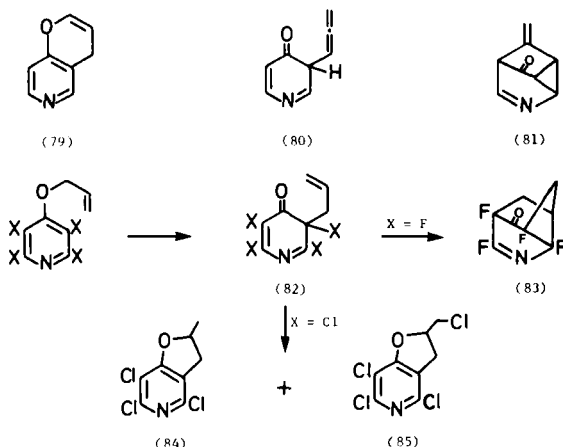


When both the 2- and 4-positions are blocked, the rearrangement of 3-propargyloxypyridines proceeds to the 2-position, and the resulting non-aromatic 2-allenyl-3-pyridone (**75**) then undergoes an interesting intramolecular Diels–Alder reaction to give **76** as the major product (78HCA2542). A similar intramolecular Diels–Alder reaction of an initial Claisen rearrangement product occurs on heating 3-allyloxy-2,4,5,6-tetrafluoropyridine, although in this case the rearrangement goes to the 4-position to give **77**, which then undergoes the intramolecular [4 + 2]-addition to give **78** in high yield (81%) (80JCS(P1)102).

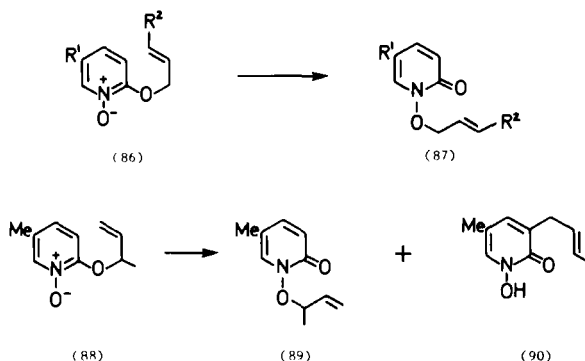


4-Substituted pyridine derivatives also take part in the Claisen rearrangement/intramolecular Diels–Alder sequence. Thus, FVP of 4-propargyloxypyridine at 550°C gives, in addition to the expected product of Claisen rearrangement and cyclization (**79**) (5%), a mixture of cyclobuta[*b*]- (35%) and cyclobuta[*c*]- (17%) pyridines. These are formed by loss of CO from the intramolecular Diels–Alder adduct (**81**) of the initial product of Claisen rearrangement (**80**) (77TL1867). Thermolysis of 4-allyloxy-2,3,5,6-tetrafluoropyridine gives **83**, again via an intramolecular Diels–Alder reaction of the initial Claisen rearrangement product (**82**, X = F), although in poor yield (80JCS(P1)102). The corresponding tetrachloro derivative, however,

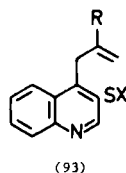
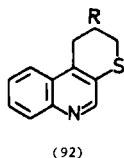
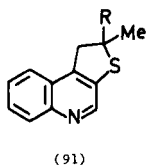
behaves differently on heating, and gives a mixture of the furopyridines **84** and **85**, formed by cyclization of the initial Claisen rearrangement product (**82**, X = Cl) (79JCS(P1)2756).



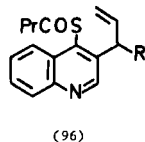
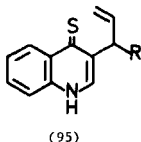
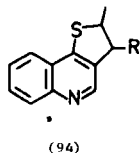
The Claisen rearrangement of 2- and 4-allyloxypyridine *N*-oxides has also been studied. Heating the 2-allyloxypyridine *N*-oxides **86** ( $R^1 = \text{H, Me}$ ;  $R^2 = \text{H, Me}$ ) at 80–100°C caused rearrangement, by an unknown mechanism, to the 1-allyloxypyridones **87**, the crotyl group migrating without allylic inversion. At higher temperatures, however, Claisen rearrangement to the 3-position supervenes. For example, the allyloxy derivative **88** gives the pyridone **89** as the minor product (20%) on heating at 137°C, together with the 1-hydroxypyridone (**90**) (75%), and a trace of the corresponding crotyloxy derivative (68JA4361). In contrast to earlier reports (67AHC(8)143) that thermal rearrangement of 4-allyloxypyridine *N*-oxide led only to tars, heating the compound under vacuum is reported to give both 3-allyl-4-hydroxypyridine *N*-oxide and 1-allyl-4-pyridone (82M11).



Claisen rearrangements of allyloxyquinolines have been known for many years (67AHC(8)143), and this work has now been extended to the corresponding allylthio derivatives. The Claisen rearrangement of 2-allylthioquinoline to 1-allylquinoline-2-thione, like the corresponding rearrangement of 2-allylthiopyridine (80JOC5221), is thermodynamically unfavorable, and heating the allylthioquinoline at 200°C for 6 hr gives only a 1% yield of Claisen rearrangement product, the major product being 2-propenylthioquinoline, formed simply by double bond isomerization (69TL1975). 3-Allylthioquinoline derivatives, however, do undergo Claisen rearrangement to the 4-position on heating to 200°C to give the cyclized products **91** and **92**, derived from the initial rearrangement product, the 3-mercaptoquinoline **93** (X = H). The product ratio is substituent dependent, and the five-membered ring (**91**, R = H) is the major product in the unsubstituted case, whereas the six-membered ring (**92**, R = Me) predominates in the methallyl case. When the rearrangement is carried out in the presence of butyric anhydride, the initial product can be trapped as its thioester (**93**, X = C<sub>4</sub>H<sub>7</sub>CO). Hydrolysis of the ester (**93**, X = C<sub>4</sub>H<sub>7</sub>CO) gives the thiol, which on heating readily cyclizes to **91** and **92** (69TL2449; 69TL2453).

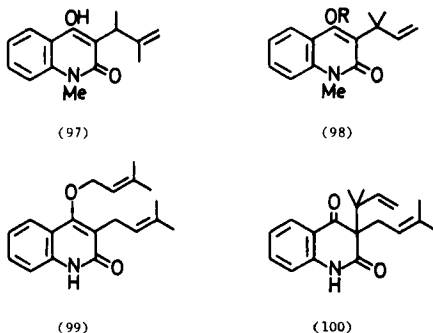


Thermolysis of 4-allylthioquinolines also leads to cyclized products. The thienoquinolines **94** formed by cyclization of the initial product of Claisen rearrangement **95**. Again, when the rearrangement was carried out in the presence of butyric anhydride, the initial product was intercepted as its butyrate (**96**); hydrolysis of the butyrate gave **95**, which cyclized on warming (66TL6399; 69TL1971).



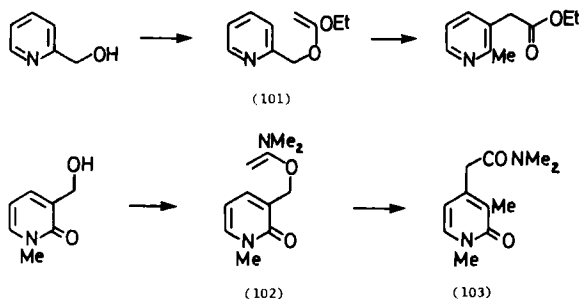
The Claisen rearrangement of 1-methyl-4-prenyloxy-2-quinolone is a key step in the biosynthesis of the alkaloid ravenoline (**97**), which is formed by a further "abnormal" rearrangement (75OR1) of the initial product (**98**, R = H) (69CC1269). The same rearrangement can be effected by heating the prenyloxyquinolone to 130–140°C, although under these conditions cyclization to a furoquinoline derivative also occurs. When the rearrangement was carried out in the presence of acetic anhydride the initial product of Claisen

rearrangement was trapped as its acetate (**98**, R = Ac) (71JCS(C)910). A Claisen rearrangement is observed on heating the quinolone alkaloid **99**, and gives the alkaloid buchapsine (**100**), although in this case the rearrangement is reversible (85TL4253).



In the isoquinoline series, 1-allyloxyisoquinoline undergoes Claisen rearrangement to 2-allylisoquinolone in high yield on heating to 250°C, and 3-allyloxyisoquinoline rearranges at 190°C to the 4-position to give 4-allylisoquinol-3-one (56%) (67JOC59). In the first example of a Claisen rearrangement in ring C of a  $\beta$ -carboline, 4-allyloxy- $\beta$ -carboline rearranges on heating at 200°C to give 3-allyl-4-hydroxy- $\beta$ -carboline (85TL2139).

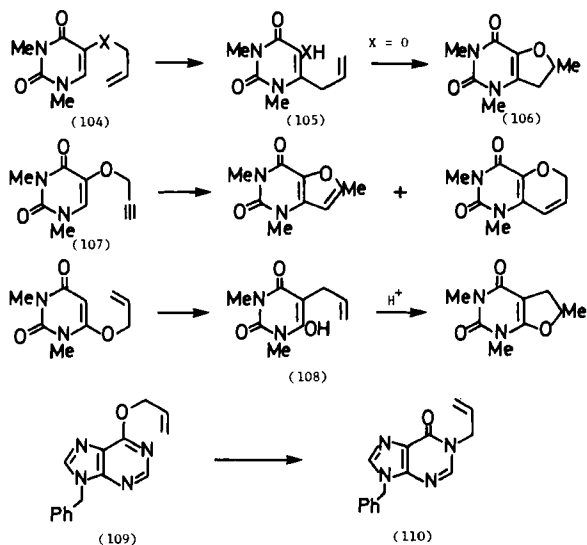
Finally, Claisen ortho ester rearrangements have been observed in pyridines and pyridones. Heating pyridine-2-methanol and triethyl orthoformate to 195°C in the presence of an acid catalyst gives a 29% yield of ethyl 2-methylpyridine-3-acetate via rearrangement of the intermediate enol ether (**101**). Pyridine-4-methanol behaves similarly to give ethyl 4-methylpyridine-3-acetate (22%), but pyridine-3-methanol gives two products (48% total), ethyl 3-methylpyridine-2-acetate and ethyl 3-methylpyridine-4-acetate, derived by competing Claisen rearrangements to the 2- and 4-positions, with a slight preference for the former (76JOC535). Heating 3-hydroxymethyl-1-methyl-2-pyridone with dimethylacetamide diethyl acetal gives pyridone **103** by Claisen rearrangement of the intermediate (**102**), and a similar rearrangement has been used as a key step in a synthesis of camptothecin (75JA159).



## B. DIAZINES, TRIAZINES, AND THEIR BENZO DERIVATIVES

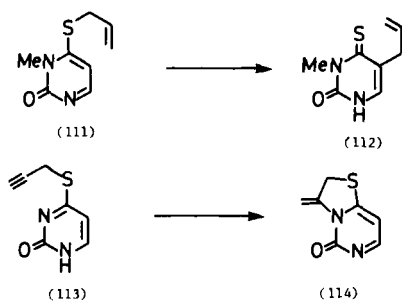
The Claisen rearrangement of simple allyloxy pyrimidines is difficult to effect. 2-Allyloxy pyrimidine itself undergoes little if any rearrangement even at 200°C (67JOC2956). The rearrangement of 4-allyloxy pyrimidine also requires high temperatures, and these results have already been summarized (67AHC(8)143). 4-Allyloxyquinazoline, however, rearranges readily on heating to 190–200°C to give 3-allylquinazolin-4-one in 75% yield (86T4873).

The Claisen rearrangement of allyloxy derivatives of 1,3-dimethyluracil also proceeds easily, and the 5-allyloxy compound **104** (X = O) gives a quantitative yield of rearrangement product **105** (X = O) on heating to 120°C. The corresponding allylaminouracil **104** (X = NH) also undergoes Claisen rearrangement, but requires a higher temperature (207°C), and the rearrangement product (**105**, X = NH) is only formed in poor yield (71JOC1251). On treatment with acid the hydroxyuracil **105** (X = O) cyclizes to the dihydrofuran derivative **106** (84H(22)2217). 1,3-Dimethyl-5-propargyloxyuracil (**107**) gives a mixture of furan and pyran derivatives on heating. The ratio of products, which are formed by competing cyclizations of the initial Claisen rearrangement product, is solvent dependent, the five-membered ring being the major product in DMF, the pyran in xylene (72JOC2858). Rearrangement of the corresponding nucleosides, 5-allyloxy- and 5-propargyloxyuridines, has also been studied. 6-Allyloxy-1,3-dimethyluracil behaves similarly to the 5-isomer, and on heating in dioxane gives the Claisen rearrangement product **108** (64%), which cyclizes on treatment with acid (84H(22)2217). Claisen rearrangements have also been observed in the purine series, 6-allyloxy-9-benzylpurine (**109**) rearranging to the *N*-allyl compound (**110**) on heating to

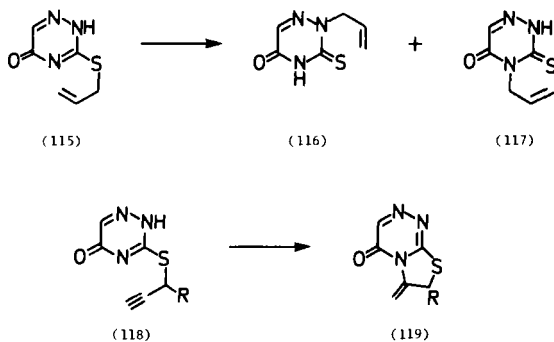


180–190°C for 6 hr (86T4873) (cf. the formation of compound **143** by rearrangement of **141**).

The *S*-allyl compound **111** undergoes Claisen rearrangement to the corresponding 5-allylthiouracil derivative (**112**) in quantitative yield on heating in benzene, although the isomeric 1-methyl derivative does not rearrange (75CC993). The *S*-propargyl derivative **113** gives the thiazolo-pyrimidone **114** on treatment with a catalytic amount of  $\text{PdCl}_2(\text{PhCN})_2$ , although the rearrangement probably involves nucleophilic attack on the Pd-complexed alkyne rather than a [3,3]-sigmatropic process (86T305).



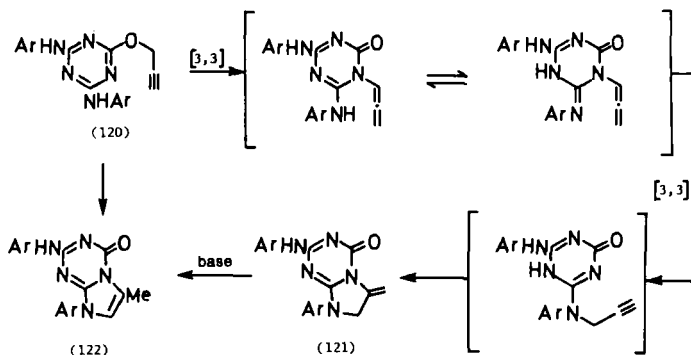
The rearrangement of *S*-allyl- (**115**) and *S*-propargyl- (**118**) 1,2,4-triazinones is also catalyzed by  $\text{PdCl}_2(\text{PhCN})_2$ . On refluxing in THF with the Pd catalyst, the *S*-allyl compound (**115**) gives a mixture of triazines **116** and **117**, derived by rearrangement to N-2 and N-4, respectively, in the ratio 12:88. In contrast, the thermal (170°C) uncatalyzed reaction is less selective, and gives approximately equal amounts of the triazines **116** and **117** (83JOC4585). Similarly, the Pd-catalyzed rearrangement of the *S*-propargyl derivative **118** also exhibits some selectivity towards N-4, and the thiazolotriazine **119** is formed as the major product (85TL1237).



Claisen rearrangements have also been observed in 1,3,5-triazines, and 2,4,6-tris(allyloxy)-1,3,5-triazine is reported to give 1,3,5-triallyltriazine-2,4,6-trione on heating to 30–70°C in the presence of a copper catalyst



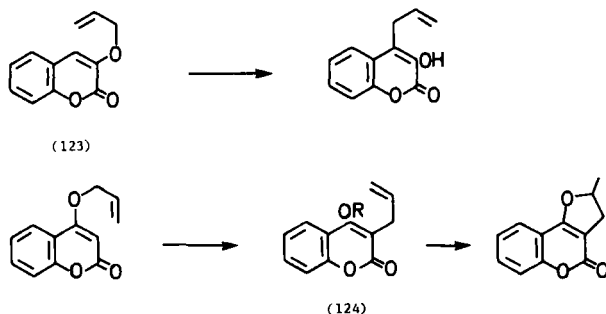
(74UKZ881). Heating the propargyloxytriazine **120** in 1,2-dichlorobenzene for 2 hr gives the imidazotriazine **121**, formed by a sequence of [3,3]-rearrangements and cyclization, as shown in Scheme 6. Heating the triazine in the same solvent for 4 hr gives the isomeric imidazotriazine **122**, which is also formed by treatment of **121** with base. Rearrangement of **120** is catalyzed by  $\text{Hg}(\text{OCOCF}_3)_2$  (80TL4731; 85T111).



SCHEME 6

### C. COUMARINS

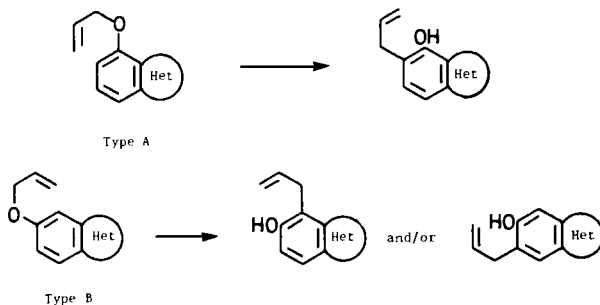
The Claisen rearrangement of several 3-allyloxy- and 4-allyloxycoumarins has been reported, and for the most part the results are entirely unexceptional. Thus 3-allyloxycoumarin (**123**) rearranges to the 4-allyl compound (79IJC(B)395; 82IJC(B)834), and several other examples of this type of rearrangement have been described (79IJC(B)333; 81IJC(B)210). In some cases the initial rearrangement product cyclizes to give a furocoumarin. In the case of 4-allyloxycoumarins, the initial product (**124**,  $\text{R} = \text{H}$ ) of Claisen rearrangement often cyclizes very easily, although this cyclization can be prevented by



carrying out the reaction in the presence of acetic anhydride, whereby the hydroxycoumarin is trapped as its acetate (**124**, R = Ac) (80G263; 80S48; 81MI1; 82TL2049; 83CI(L)827; 83MI1).

## V. Claisen Rearrangements in the Benzene Ring of Benzo-Fused Systems

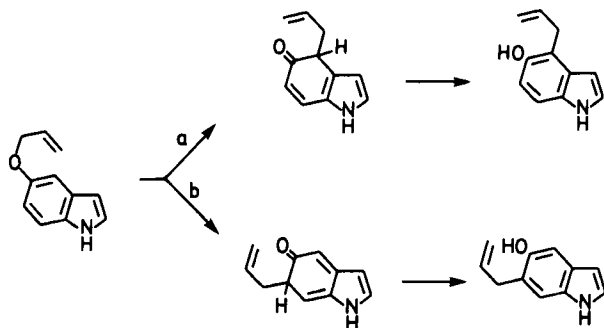
Claisen rearrangements in the benzene ring of benzo-fused five- and six-membered heterocyclic compounds fall into two distinct categories. The starting materials for the first, designated Type A, contain the allyl ether substituent at a position adjacent to the ring junction, and are therefore for the most part unremarkable and rearrange as expected, with the heterocyclic ring effectively blocking the alternative direction of rearrangement. The second class, Type B, in which the allyl ether side chain in the starting material is  $\beta$  to the ring junction, are more interesting in that, in principle, rearrangement can occur in two directions. In practice, however, the Claisen rearrangement of such allyl ethers of bicyclic heteroaromatic systems exhibits a high degree of regioselectivity.



Regioselectivity in the Claisen rearrangement of other bicyclic aromatic allyl ethers is not unknown. Indeed, the rearrangement of 2-allyloxynaphthalene to give exclusively 1-allyl-2-hydroxynaphthalene is described in Claisen's original paper (12CB3157). Several rationalizations can be advanced for this observed regioselectivity. It is well known that in naphthalene the 1,2- and 2,3-bond lengths are not equal (1.360 and 1.415 Å, respectively), and this bond alternation, often referred to as *partial bond fixation*, is found in nearly all fused aromatic (85MI1) and heteroaromatic (85MI2) systems. Therefore, on a purely descriptive basis, the bond localization observed in naphthalene would lead one to expect that the Claisen rearrangement of 2-allyloxynaphthalene should proceed selectively to the 1-position. Similarly, the bond localization observed in bicyclic heteroaromatic systems would lead to the prediction that

the Claisen rearrangement of 5-allyloxyindole, for example, should selectively occur to the 4-position (Scheme 7, Path a), as is indeed the case (q.v.).

The results can also be rationalized using the valence bond model, based on the "product" stability argument. In the case of the Claisen rearrangement, the "product" to consider is the dienone initially formed in the [3,3]-sigmatropic process, and the two possible dienones for the rearrangement of 5-allyloxyindole are shown in Scheme 7. It is immediately apparent that the intermediate leading to the 4-allyl product is of lower energy than that leading to the 6-substituted indole, by virtue of the fact that it retains some aromatic stabilization. Such arguments do have some validity, especially if extended to transition states, and have recently been summarized in the suggestion that the Claisen rearrangement of aromatic allyl ethers (and for that matter aromatic electrophilic substitution) occurs via a transition state which most closely resembles the valence bond resonance form of lowest energy (82CC1333).

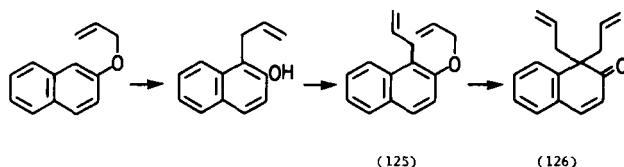


SCHEME 7

Although the above rationalizations satisfactorily explain the experimental facts, in dealing with pericyclic processes they are somewhat superficial. Since the reaction is orbital controlled, the electron distribution in the molecular orbitals (MO) must be considered, and for the relative rates of two processes, it is the frontier orbitals that are the most important (76MI1). The coefficients of the highest occupied molecular orbital (HOMO) and the closely related frontier electron population have been calculated for unsubstituted aromatic and heteroaromatic systems. For the same examples as above, one finds that for naphthalene the coefficient is much larger at C-1 than at C-3, and for indole, frontier electron population is larger at C-4 than at C-6. Thus, assuming that this also holds for the substituted compounds, the Claisen rearrangement proceeds toward the site with the higher orbital coefficient, and it is comforting to find that the MO approach leads to the same answer as the valence bond approach (as it also does in many other situations, of course!). In

passing, it should also be noted that both the valence bond and MO arguments advanced to explain the regioselectivity of the Claisen rearrangement are in essence the same as those used to explain the direction of aromatic electrophilic substitution reactions (76M11; 82CC1333).

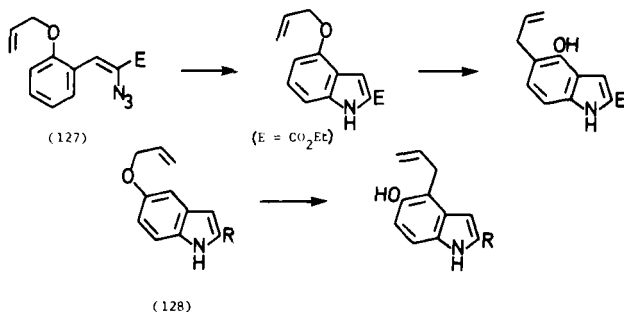
Whatever the exact explanation, the effects of bond localization/orbital control on the direction of the Claisen rearrangement are very powerful, as is demonstrated by the fact that rearrangement of 1-allyl-2-allyloxynaphthalene (**125**) still proceeds to the 1-position to give the nonaromatic naphthalenone **126** (64CI(L)1801).



As in Sections II and IV, the following discussion is organized by ring system. Rearrangements of both Types are included, but particular emphasis is placed on rearrangements of Type B in which there is a regiochemical problem.

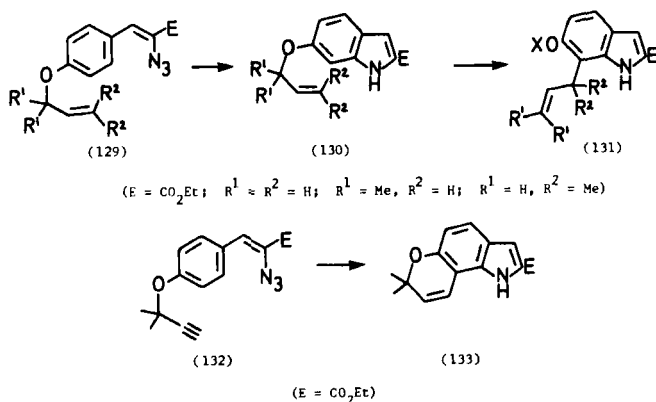
#### A. INDOLES, BENZOFURANS, BENZOTHIOPHENES, AND BENZAZOLES

Ethyl 4-allyloxyindole-2-carboxylate undergoes the expected Claisen rearrangement in 76% yield on heating in bromobenzene (156°C). One interesting feature of the reaction is that the indole is prepared by thermolysis of the azide **127** at 110°C, so that, when the azide was heated at 156°C, concomitant indole formation and Claisen rearrangement occurred to give ethyl 5-allyl-4-hydroxyindole-2-carboxylate directly in 77% yield (84JCS(P1)1333). The first example of a Type B Claisen rearrangement in indoles was reported by Julia, who described the regioselective rearrangement of 5-allyloxyindole (**128**,

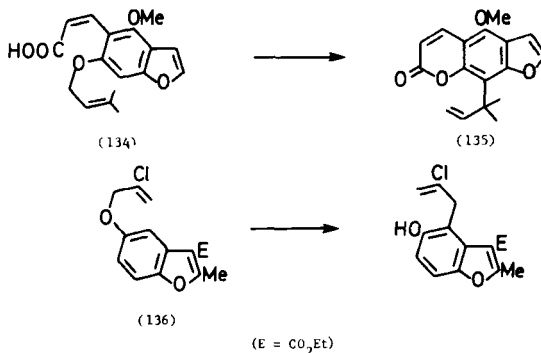


R = H) and the corresponding ester (**128**, R = CO<sub>2</sub>Et) to the 4-allyl derivatives in high yield (73BSF2046).

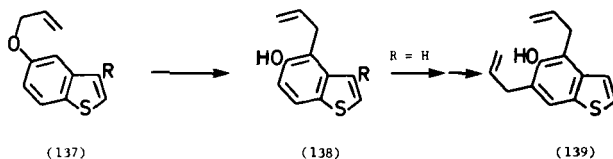
Most of the work on the regioselective Claisen rearrangement in indoles has been done with 6-hydroxyindole derivatives. The indoles **130**, prepared by thermolysis of the azides **129**, rearrange selectively to the 7-allylindoles (**131**, X = H). In the case of the 6-(3,3-dimethylallyloxy) derivative (**130**, R<sup>1</sup> = H, R<sup>2</sup> = Me), however, rearrangement has to be carried out in the presence of acetic anhydride to prevent the abnormal Claisen rearrangement and gives the indole **131** (X = Ac, R<sup>1</sup> = H, R<sup>2</sup> = Me). Again, concomitant indole formation and Claisen rearrangement are observed when the azides **129** themselves are heated in bromobenzene. Subsequently it was found that the Claisen rearrangement of the 1,1-dimethylallyl derivative occurred at lower temperatures, and the unrearranged indole (**130**, R<sup>1</sup> = Me, R<sup>2</sup> = H) could not be isolated even after refluxing the corresponding azide in toluene for a short time. When the 7-allyl-6-allyloxyindole **131** (X = allyl, R<sup>1</sup> = R<sup>2</sup> = H), prepared by allylation of the corresponding 6-hydroxyindole, was heated in bromobenzene, no further rearrangement occurred. Heating the 6-propargyloxyazide **132** in toluene at 110°C caused cyclization to the indole and regioselective Claisen rearrangement, followed by cyclization to give the pyranoindole **133** (84JCS(P1)1333). The Claisen rearrangement of 6-allyloxyindole derivatives has been used as a method of selectively introducing a linalyl substituent into the indole 7-position (84JCS(P1)1333; 86TH1), and as a key step in the synthesis of the alkaloid murrayaquinone-B (85CC1391).



Heating the 6-prenyloxybenzofuran **134** in a mixture of xylene and acetic anhydride causes Claisen rearrangement to the 7-position and cyclization to give the furocoumarin natural product furopinnarin (**135**) in 80% yield (82IJC(B)472). The 5-allyloxy derivative **136** undergoes regioselective Claisen rearrangement to the 4-position with no trace of any rearrangement to the 6-position (78JHC43).

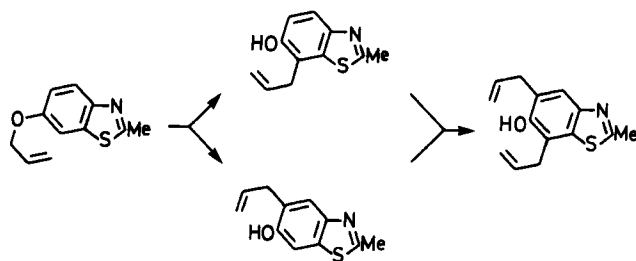


In the benzothiophene series, 4-allyloxy-2-methyl- and 7-allyloxy-2-methylbenzothiophene both undergo the expected rearrangement in high yield on heating in DMA for 3–4 hr (72JCS(P1)2593; 73JCS(P1)1196). Again, however, the more interesting results are obtained with 5- and 6-allyloxy derivatives. 5-Allyloxybenzothiophene (**137**, R = H) and the 3-methyl analogue (**137**, R = Me) both undergo regioselective Claisen rearrangement on heating to give the corresponding 4-allyl-5-hydroxy compounds (**138**) (55JA5939; 69JCS(C)1). When the hydroxybenzothiophene (**138**, R = H) was subsequently reacted with allyl bromide and the resulting allyl ether resubjected to the Claisen rearrangement conditions of boiling in DMA, a second rearrangement occurred to give a product which was assigned the structure **139** (55JA5939). That the second rearrangement should occur at the electronically unfavored position is in direct contrast to the rearrangement of 1-allyl-2-allyloxynaphthalene (**125**), discussed previously. In parallel with the rearrangement of 6-allyloxyindoles, 6-allyloxybenzothiophene undergoes regioselective Claisen rearrangement to 7-allyl-6-hydroxybenzothiophene with no evidence for competing rearrangement to the 5-position (78JCR(S)10).

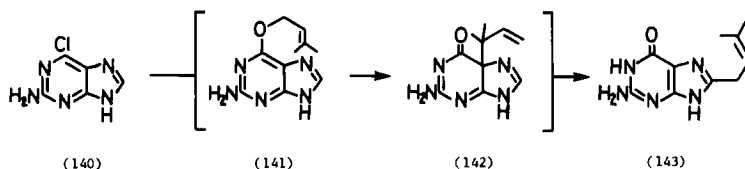


In contrast to 6-allyloxyindoles and -benzothiophenes, Claisen rearrangement of 6-allyloxy-2-methylbenzothiazole is reported to give both possible products, although it is highly selective (20:1) in favor of rearrangement to the 7-position. The rearrangement products were separated as their picrates, separately alkylated with allyl bromide, and resubjected to the Claisen rearrangement conditions to give the same product, which was assigned as 5,7-diallyl-6-hydroxybenzothiazole (Scheme 8) (41CB1407; 43MI1). This result is

in contrast to the related 7-allyl-6-allyloxyindoles, which did not undergo a second rearrangement. In benzisothiazole, however, rearrangement is regio-specific, 5-allyloxy-2-methylbenzisothiazole giving the 4-allyl isomer exclusively (80JCR(S)197). Reaction of the chloropurine derivative **140** with the sodium salt of 3,3-dimethylallyl alcohol gives a high yield of the 8-prenyl compound (**143**), presumably formed via the allyl ether **141**, which undergoes an interesting Claisen rearrangement to the ring junction position to give **142**, followed by a second [3,3]-rearrangement (73JA7174). When the 8-position is blocked with a methyl group, the major pathway involves rearrangement to N-3 (76JOC568).

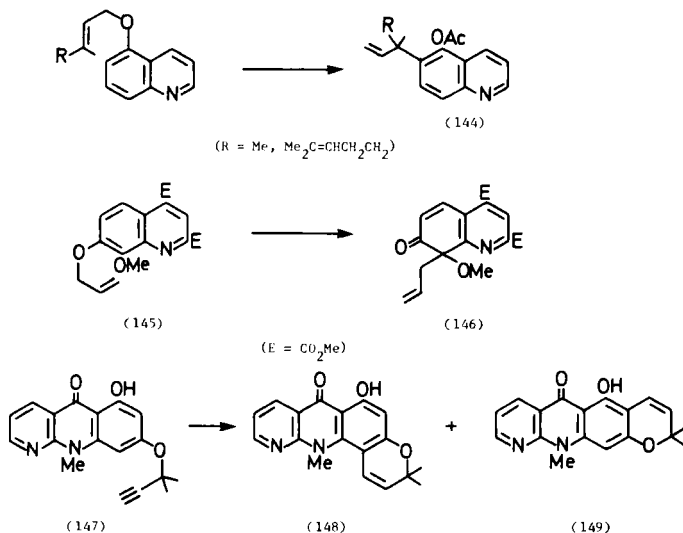


SCHEME 8



## B. QUINOLINES

Rearrangement of 5-prenyloxy- and 5-geranyloxyquinolines in boiling acetic anhydride in the presence of potassium acetate or sodium acetate gives the quinolines **144** in good yield. The acetylating conditions are essential to prevent the abnormal Claisen rearrangement from occurring (76JOC3026). The question of regioselectivity arises with 7-hydroxyquinoline derivatives, and 7-allyloxyquinoline gives only 8-allyl-7-hydroxyquinoline when heated in a sealed tube at 230°C (40M11). The powerful factors which control the rearrangement of naphthalene (**125**) also operate in quinolines, the 7-allyloxyquinoline **145** rearranging to the nonaromatic derivative **146** on heating (81TH1). The rearrangement of benzonaphththyridine propargyl ether (**147**) is less selective, however, and gives a 2:1 mixture of fused pyrans **148** and **149**, formed by Claisen rearrangement and cyclization (83JCS(P1)219).

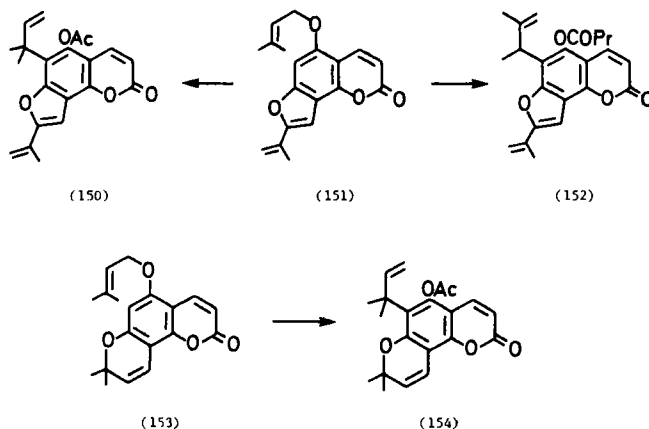


### C. COUMARINS, FLAVONES, AND XANTHONES

Of all the Claisen rearrangements of heteroaromatic allyl ethers, those involving coumarins have been the most widely investigated, notably by Murray and his group at Glasgow. The reason for this intense interest is that coumarins that are oxygenated at C-7, and contain isoprenoid units at C-8 or C-6, are frequent constituents of higher plants, and are synthetically accessible by the Claisen rearrangement. Since the background to this work is extensively covered in a monograph (82MI2), only a few key examples are included here. Although, for the reasons outlined above, the rearrangement of 7-hydroxy derivatives has been the most widely studied, the rearrangement of 5-, 6-, and 8-allyloxycoumarins has also received some attention.

All the work on the rearrangement of 5-allyloxycoumarins is also directed toward the synthesis of natural products. Thus, heating the 5-(3,3-dimethylallyloxy)furocoumarin **151** in acetic anhydride in the presence of sodium acetate gives the Claisen rearrangement product **150** in quantitative yield. The role of the acetic anhydride is, as usual, to prevent the abnormal Claisen rearrangement. Interestingly, however, when the starting allyl ether was heated in a mixture of DMA and butyric anhydride, the abnormal product **152** is formed, even in the presence of the trap (83T3159). Similarly, heating the prenyloxypyranocoumarin **153** gives the Claisen rearrangement product in excellent yield (84T3133). Both products **150** and **154** were subsequently elaborated into naturally occurring coumarins.





The 1,1-dimethylallyl ether **156** ( $R = H$ ) rearranges as expected on heating at  $114^{\circ}\text{C}$  to give coumarin **155** (75T2960). The 6-methoxy derivative (**156**,  $R = \text{OMe}$ ), in contrast, rearranges to the nonaromatic dienone **157**, even at room temperature, on attempted chromatography on silica gel; the rearrangement is presumably facilitated by steric crowding in the starting material (75T2966). In contrast to 5-(3,3-dimethylallyloxy)furo- and -pyranocoumarins **151** and **153**, the rearrangement of 5-(3,3-dimethylallyloxyl)-7-methoxy- (or acetoxy)-coumarins (**159**) produces anomalous results. Although heating the allyl ether **159** ( $R = \text{Me}$ ) in acetic anhydride in the presence of sodium acetate gives the expected product (**158**), heating in acetic anhydride alone leads to **160** ( $R = \text{Me}$ ,  $X = \text{Ac}$ ) of para-Claisen rearrangement (75OR1), despite the fact that the ortho- position is free (84T5229). Likewise, heating the ether **159** ( $R = \text{Me}$ ) in a mixture of DMA and butyric anhydride leads exclusively to the para-rearrangement product (**160**,  $R = \text{Me}$ ,  $X = \text{COPr}$ ) (75T2960; 78T1411), and rearrangement of the acetoxycoumarin **159** ( $R = \text{Ac}$ ) in neat acetic anhydride gives the para product (**160**,  $R = X = \text{Ac}$ ) (84T3129). Not surprisingly, when the ortho (6-) position is blocked with, for example, an ester group, rearrangement also occurs to the para (8-) position (78IJC(B)856). Similarly, heating the furocoumarin **161** causes rearrangement to the unblocked 8-position (79T697).

As expected on the basis of bond alternation, 6-allyloxycoumarins rearrange selectively to the 5-position. Thus, 6-allyloxy-4-methoxycoumarin gives 5-allyl-4-methoxy-6-hydroxycoumarin on heating (73JIC813), and 6-(3,3-dimethylallyloxy)-7-methoxycoumarin rearranges to 6-acetoxy-5-(1,1-dimethylallyl)-7-methoxycoumarin when heated in acetic anhydride containing sodium acetate (84T5229). In contrast, however, Claisen rearrangements of 6-cinnamyloxy- and 6-(3,3-dimethylallyloxy)-4-methylcoumarins are reported to proceed to the 7-position (78IJC(B)856; 78IJC(B)1039).

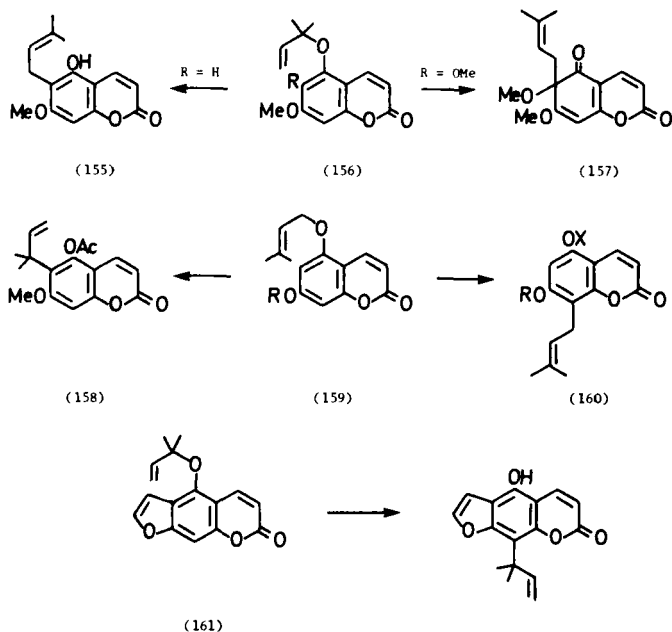
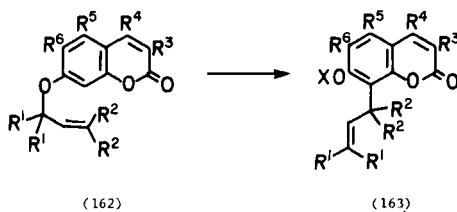


TABLE III  
SYNTHESIS OF "ANGULAR" COUMARINS



	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	X	Reference
a	H	H	Ph	H	H	H	H	a
b	H	H	Ph	OMe	H	H	H	b
c	H	H	H	Ph	H	H	H	c
d	H	Me	H	H	OMe	H	COPr	d
e	H	Me	H	H	H	OMe	COPr	e
f	Me	H	H	H	<i>O</i> -Prenyl	H	H	f
g	H	Me	H	H	OMe	COCH=CM <sub>2</sub>	g	h

<sup>a</sup> 77JJC(B)1094.

<sup>b</sup> 77JJC(B)1097.

<sup>c</sup> 74IJC292.

<sup>d</sup> 70T4667.

<sup>e</sup> 83T3163.

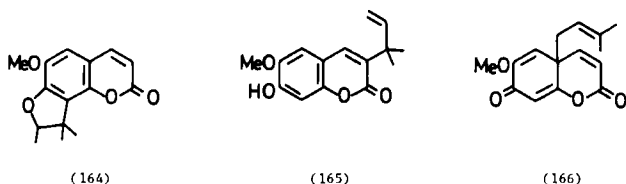
<sup>f</sup> 75T2960.

<sup>g</sup> Initial product cyclizes onto Me<sub>2</sub>C=CH of 6-substituent.

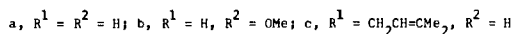
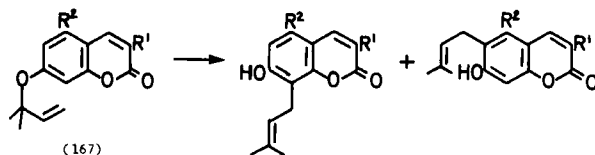
<sup>h</sup> 73T2943.

In the main, 7-allyloxycoumarins (**162**) undergo regioselective Claisen rearrangement to give 8-allylcoumarins (**163**), and extensive use of this has been made in the synthesis of naturally occurring "angular" coumarins. Some examples are shown in Table III. It is noteworthy that heating the coumarin **162f** at 130°C causes exclusive rearrangement of the 7-(1,1-dimethylallyloxy) group in preference to the 5-(3,3-dimethylallyloxy) group.

The rearrangement of 7-(3,3-dimethylallyloxy)coumarins **162d** and **162e** was carried out in the presence of butyric and acetic anhydrides, respectively, and gave the normal Claisen rearrangement products in very high yield. In the absence of the acylating agents, the coumarin **162e** gave a mixture of products, including the cyclized dihydrofurocoumarin **164** and the 3-(1,1-dimethylallyl)coumarin **165**. The latter product is formed by an interesting out-of-ring rearrangement, and presumably involves a triple [3,3]-process via the initial Claisen rearrangement product and the intermediate **166** (71T871). Similarly, thermal rearrangement of the coumarin **162d** in the absence of acylating agents gives a mixture of products (73IJC1126).

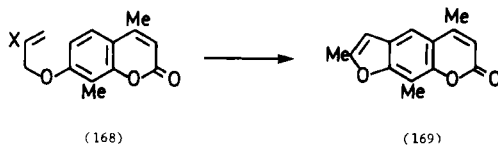


In some cases the Claisen rearrangement of 7-allyloxycoumarins is not totally regioselective. Thus, heating the coumarin **167a** to 130°C gives a 74:14 mixture of products arising from rearrangement to the 8- and 6-positions, respectively. The rearrangement of the corresponding 3-methoxy derivative (**167b**), however, is regioselective towards the 8-position (71T1247), although heating **167c** gives a 50:10 mixture of products resulting from rearrangement to the 8- and 6-positions (83IJC(B)408).

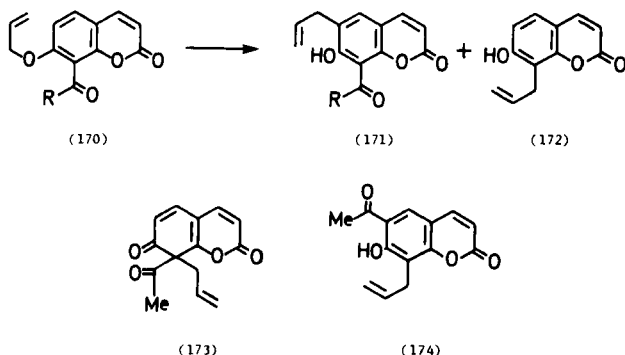


Higher yields of rearrangement to the 6-position are obtained when the 8-position is blocked. Thus 7-allyloxy-4-hydroxy-8-methyl-3-phenylcoumarin rearranges (50%) to the 6-allyl-7-hydroxy compound on heating (75JIC45). The blocked haloallylcoumarins **168** (X = Cl or Br) undergo Claisen re-

arrangement to the 6-position, followed by cyclization to give the psoralen **169** (79JOC2176; 80JOC738), and the corresponding thio-Claisen rearrangement has been used to prepare sulfur analogues of psoralens (80JHC911).

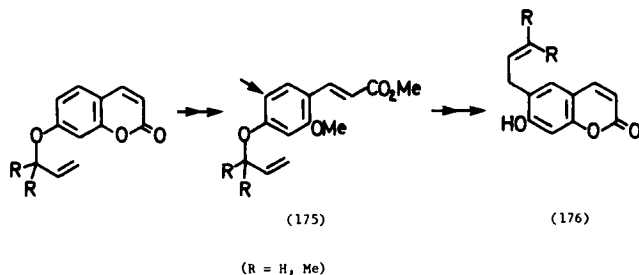


However, the preference for the Claisen rearrangement of 7-allyloxycoumarins to rearrange to the 8-position is strong, and blocking groups do not always prevent rearrangement to this position. For example, heating 7-allyloxy-8-formyl-4-methylcoumarin (**170**, R = H) gave an equal amount of the coumarins **171** (R = H) and **172**, the latter being formed by Claisen rearrangement to the blocked 8-position, followed by formal loss of CO. The rearrangement of the corresponding 8-acetylcoumarin **170** (R = Me) is more complex. In addition to the coumarins **171** (R = Me) and **172**, formed by rearrangement to the 6-position and to the 8-position with deacetylation, respectively, the reaction gave the dienone **173** and the acetyl migration product **174** (83JOC2709).

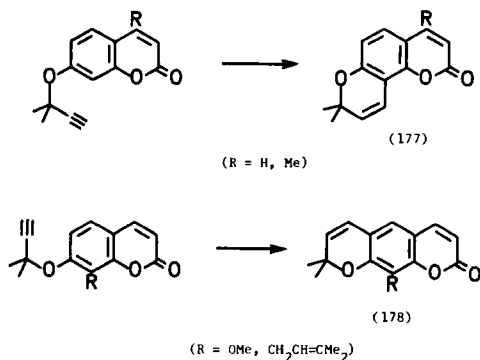


As an alternative to blocking the 8-position, selective rearrangement to the 6-position, and hence access to naturally occurring "linear" coumarins, can also be achieved by prior disruption of the coumarin nucleus to vinylogous coumaric acid derivatives. These derivatives (**175**) undergo regioselective Lewis acid-catalyzed Claisen rearrangement in the direction indicated; subsequent lactonization then gives the linear coumarins **176** (86CC182; 86CC750; 86CC1264).

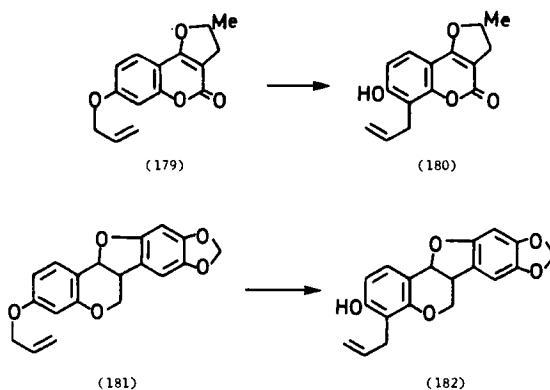
The Claisen rearrangement of 7-propargyloxycoumarins has also been investigated. In the absence of substitution in the 8-position, rearrangement proceeds smoothly to that position, and is followed by cyclization to give



angular pyranocoumarins **177** (69TL1369; 84M327). When the 8-position is blocked, however, rearrangement proceeds to the 6-position, and linear pyranocoumarins **178** result (69TL1369; 731JC983).

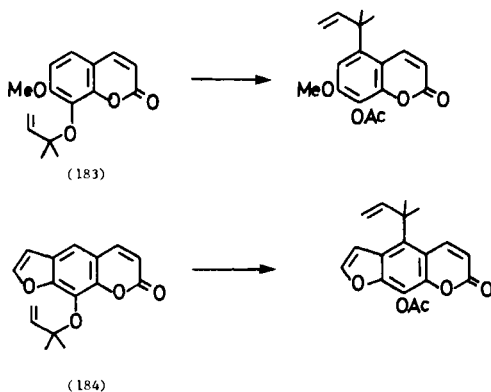


7-Allyloxy fused coumarin derivatives also undergo regioselective Claisen rearrangement. This is exemplified by the rearrangement of **179** into **180** (79JIC56). Interestingly, the rearrangement of the chromane **181**, in which no influence of the second ring on bond localization is possible, is also regioselective, and gives compound **182**, which was subsequently converted

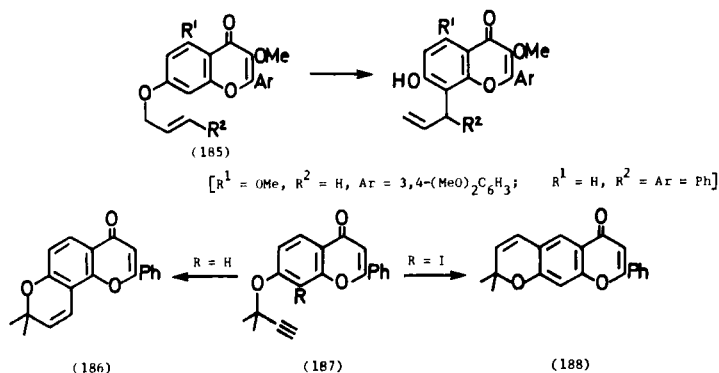


into the natural product cabenegrin A-I on heating in diethylaniline (82TL3859).

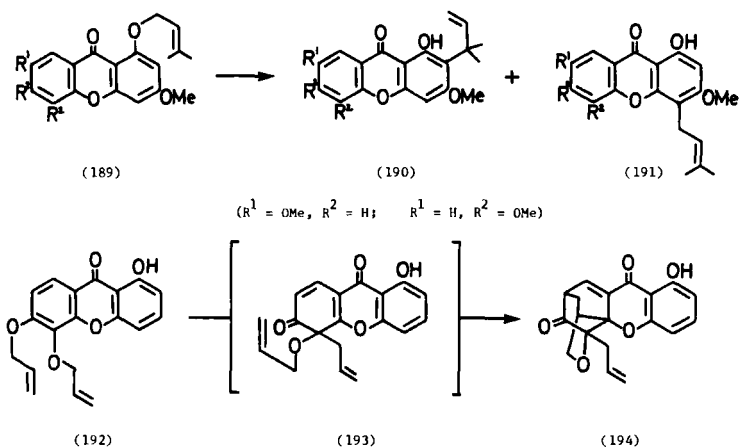
Rearrangement of simple 8-allyloxycoumarins proceeds as expected to the 7-position. 8-Allyloxycoumarin itself rearranges to 7-allyl-8-hydroxycoumarin (85JHC649). When the 7-position is blocked, however, as in the coumarins **183** and **184**, heating in acetic anhydride in the presence of sodium acetate causes para-Claisen rearrangement to the 5-position (84T5225; 84T5229).



7-Allyloxyflavones **185** undergo regioselective Claisen rearrangement on heating to give the expected 8-allyl derivatives (65CB114; 78PIA(A)389), and the corresponding 7-propargyloxy flavone **187** ( $R = H$ ) rearranges with subsequent cyclization to give the angular pyranoflavone **186**. When the 8-position is blocked by an iodine atom, thermolysis of flavone **187** ( $R = I$ ) gives the linear pyranoflavone **188**, the iodine apparently being lost during the reaction (82IJC(B)101).



Claisen rearrangement of 1-(3,3-dimethylallyloxy)xanthenes **189** gives mixtures of products **190** and **191**, which result from normal ortho- and para-rearrangement, respectively. The para product is the major product (65T2653; 66JCS(C)2265). Cross-over experiments confirmed that product **191** was formed by an intramolecular para-Claisen rearrangement (68JOC 1259). In an interesting biogenetically inspired approach to the morellins, the 5,6-diallyloxyxanthone **192** was heated in decalin to effect regioselective Claisen rearrangement to the 5-position, followed by intramolecular Diels–Alder reaction of the intermediate **193** to give **194** (71CC966).



## VI. Conclusion

The Claisen rearrangement of heteroaromatic allyl ethers shows many similarities to the rearrangement of simple benzenoid aromatic allyl ethers. Mechanistically, the reactions are for the most part genuine [3,3]-sigmatropic rearrangements, although the presence of nitrogen in the aromatic ring does allow alternative pathways to operate, and hence more than one product may be formed. However, these alternative products are usually easily rationalized on mechanistic grounds. One other difference between the Claisen rearrangement of heteroaromatic allyl ethers (or thioethers) and their benzene counterparts is that the rearrangement product is often more stable in the -one form than as the hydroxy (or mercapto) heteroaromatic compound.

The Claisen rearrangement has been widely used in the synthesis of natural heterocyclic products. Although much of this work has been in the coumarin series, there are now several alkaloid syntheses in which the Claisen rearrangement features as a key step. Indications are that the Claisen rearrangement will continue to hold an important role in organic chemistry.

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# The Synthesis of Natural Heterocyclic Products by Hetero Diels–Alder Cycloaddition Reactions

TETSUJI KAMETANI

*Institute of Medicinal Chemistry,  
Hoshi University, Tokyo, Japan*

SATOSHI HIBINO

*Faculty of Pharmacy and Pharmaceutical Sciences,  
Fukuyama University, Fukuyama, Hiroshima, Japan*

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## I. Introduction

The Diels–Alder reaction is one of the most common and elegant methods for the construction of carbocyclic six-membered ring systems. Especially for the synthesis of polycyclic natural products, it presents an unrivaled opportunity for the regioselective and stereospecific introduction of multiple centers of configuration. Moreover, it has been known that reactive species can be generated in which one or two of the atoms of the dienophile and/or the diene carbon have been replaced by hetero atoms, and that cycloadditions of these systems with dienophiles or conjugated dienes yield a variety of six-membered heterocyclic compounds. A comprehensive review of Diels–Alder cycloaddition reactions with heterodienophiles appeared in 1982 (82T3087). Recent reviews of Diels–Alder reactions with heterodienes containing one or two hetero atoms appeared in 1983 (83T2869) (azadienes), 1975 (75CRV651) (oxadienes), and 1983 (83CSR53) (nitrosoalkenes). In this article, we describe the utility of inter- and intramolecular [4 + 2]-cycloaddition reaction using heterodienophiles of heterodienes. Accordingly, this article is restricted to the synthesis of heterocyclic natural products and does not discuss the synthesis of heterocyclic natural products by all-carbon Diels–Alder reactions.

## II. Diels–Alder Reactions Using Heterodienophiles

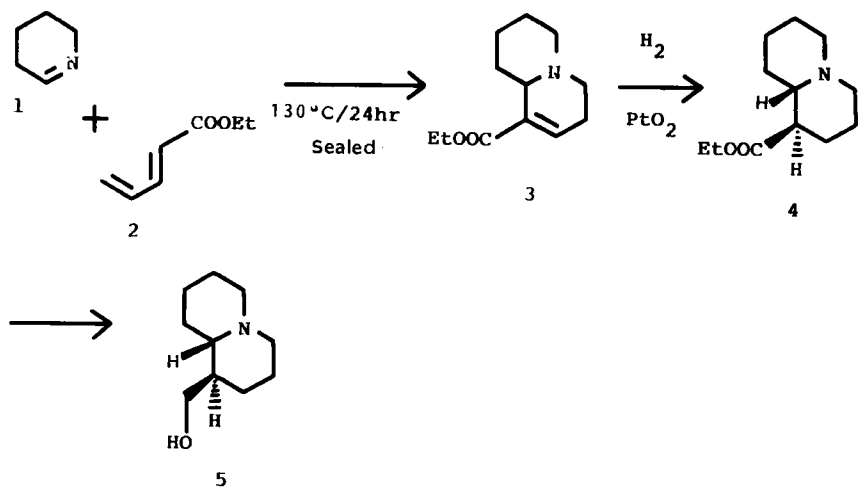
### A. C=N DIENOPHILES

#### 1. Intermolecular Cycloaddition Reactions

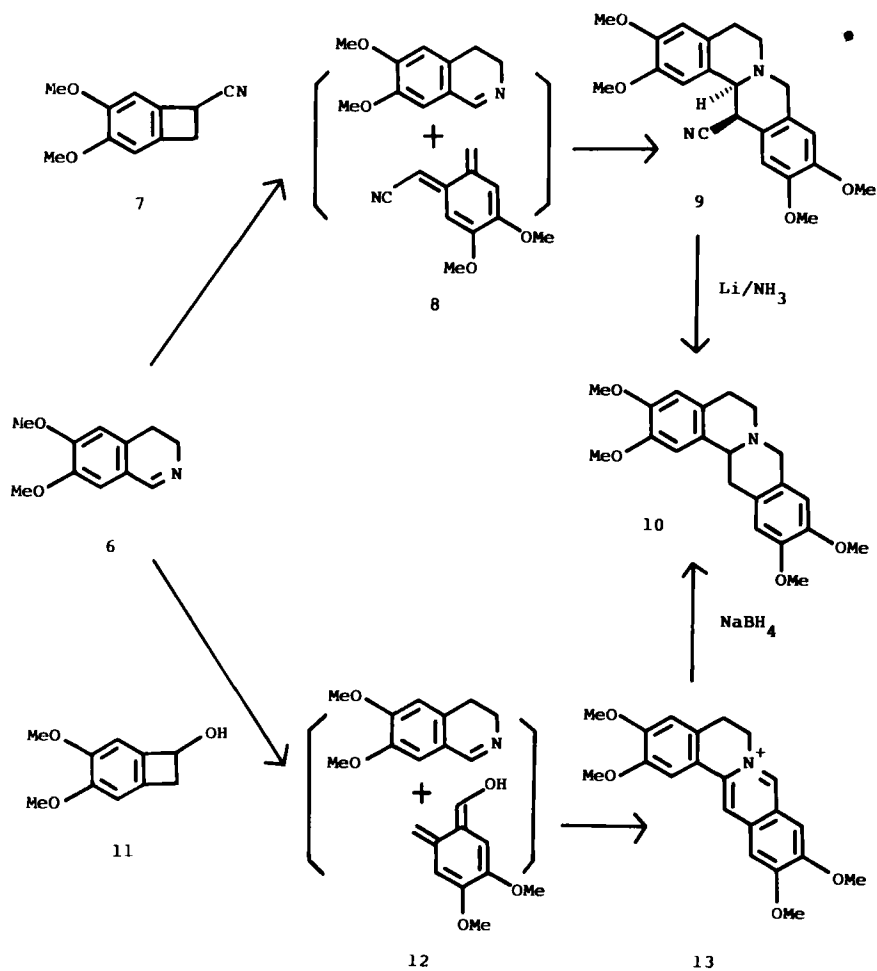
The use of imines as the dienophilic components of [4 + 2]-cycloaddition reactions was reviewed in 1979 (79H949) and 1982 (82T3087).

Bohlmann and co-workers (67CB2742) have added imine **1** to ethyl 2,4-pentadienoate (**2**) to afford adduct **3** in fair yield. Adduct **3** was further transformed into the quinolizidine alkaloid lupinine (**5**), as shown in Scheme 1.

The Kametani group found that the concept of “retro mass spectral synthesis” served to suggest synthesis of heterocyclic natural products such as isoquinoline and indole alkaloids (76ACR319). Some applications of this methodology have given rise to thermolytic cycloaddition of several imines with *o*-quinodimethanes, produced *in situ* from substituted benzocyclobutenes. On the basis of this retro synthetic analysis, a total synthesis of xylopinine **10** by use of 1-cyano- and 1-hydroxybenzocyclobutenes was examined (Scheme 2). Heating an equimolar amount of 1-cyanobenzocyclobutene (**7**) and the 3,4-dihydroisoquinoline **6** at 150–160°C gave 13-cyanoprotoberberine (**9**) in 80–88% yield (74JOC447). Reductive decyanation



SCHEME 1

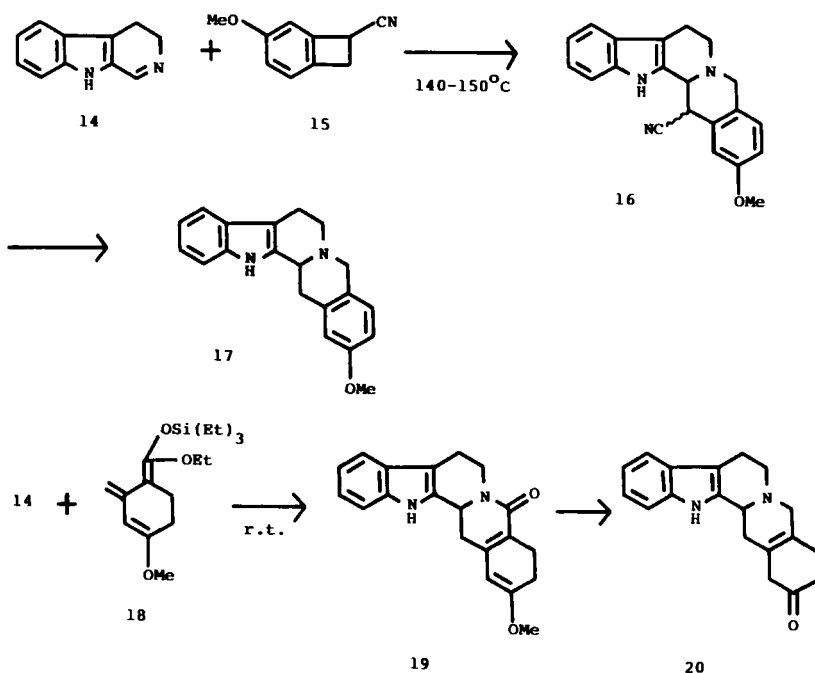


SCHEME 2



with lithium and liquid ammonia in the presence of isopropyl alcohol afforded xylopinine (**10**) (85%) (75JCS(P1)737). Similarly, a mixture of the benzocyclobutenol **11** and imine **6** in benzene was heated to give the protoberberine **13** (56%), which was reduced with sodium borohydride to afford **10** (74JCS(P1)1712).

Intermolecular cycloaddition of 1-cyanobenzocyclobutene **15** to 3,4-dihydro- $\beta$ -carboline (**14**) was effected at 140–150°C without solvent to give regioselectively the 14-cyano-hexadehydro-yohimbane **16** (85%). This was decyanated by treatment with lithium and liquid ammonia/isopropyl alcohol to afford the hexadehydro-yohimbane **17** (Scheme 3) (74T1053).

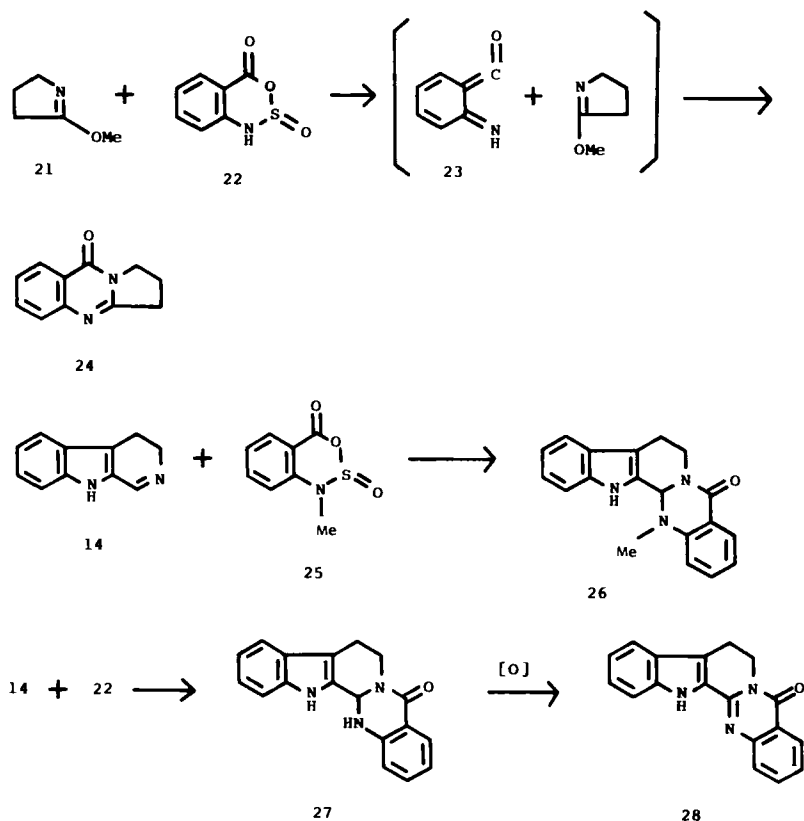


SCHEME 3

Danishefsky has used the imine–diene cycloaddition reaction (Scheme 3) (85TL5983). Reaction of Hagemann's ester **18** with dihydro- $\beta$ -carboline **14** in chloroform without catalyst afforded 50% of the pentacyclic lactam **19**. Reduction of **19** with lithium aluminum hydride followed by acidic hydrolysis gave the known yohimbine derivative **20**.

The Kametani group further investigated quinazolone synthesis by cycloaddition of iminoketene with imines based on the concept of retro mass spectral synthesis and applied it to the total syntheses of deoxyvasicinone (**24**),

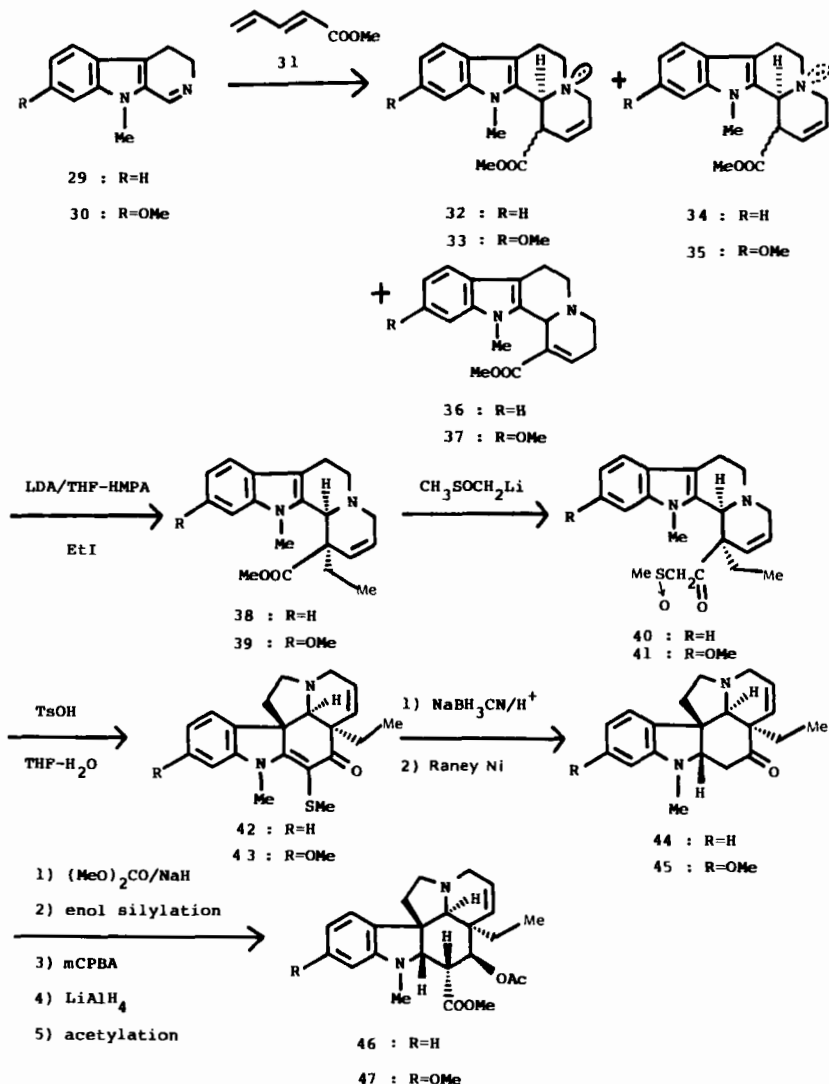
evodiamine (**26**), and rutecarpine (**28**) (76H23; 76JA6186). Heating anthranilic acid with thionyl chloride in dry benzene under reflux (Scheme 4) gave the unstable sulfinamide anhydride **22**. The reaction of **22** with imino ether **21** in dry benzene at room temperature afforded regioselectively deoxyvasicinone (**24**) in good yield. Heating *N*-methylantranilic acid with thionyl chloride gave *N*-methylsulfinamide anhydride **25**, which, on treatment with 3,4-dihydro- $\beta$ -carboline (**14**), evolved sulfur dioxide to produce evodiamine (**26**) regiospecifically (65%). Finally, rutecarpine (**28**) (80%) was also obtained in one step by treatment of the sulfinamide anhydride **22** with imine **14** in dry benzene at room temperature, followed by a spontaneous dehydrogenation of adduct **27**.



SCHEME 4

Langlois and co-workers (82CC1118; 85JOC961) succeeded in the total synthesis of vindrosine (**46**) and vindoline (**47**) by the imino Diels–Alder cycloaddition using dihydro- $\beta$ -carbolines and the diene shown in Scheme 5.

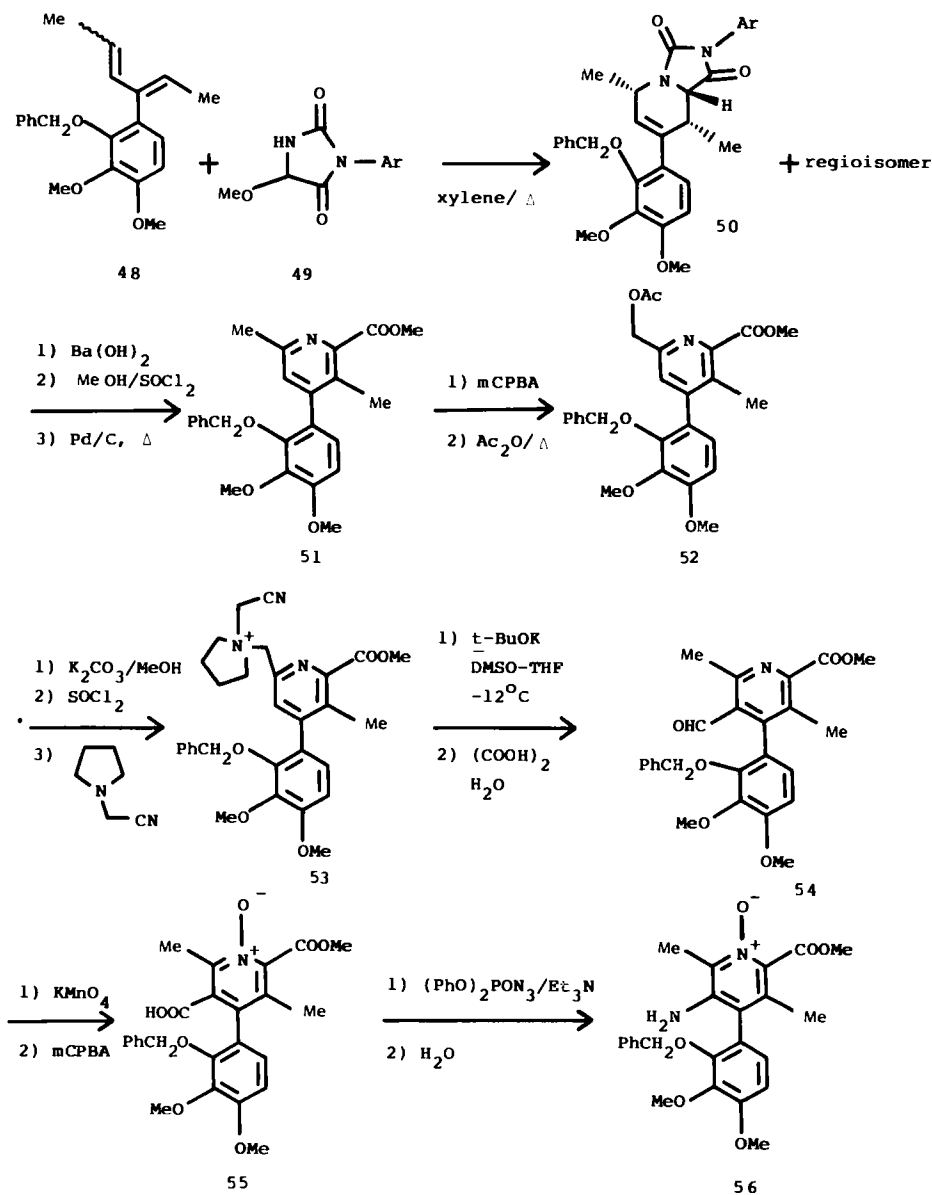
*N*-Methyldihydro- $\beta$ -carboline (**29**) was subjected to the imino Diels–Alder reaction in the presence of methyl pentadienoate (**31**) to give a mixture of adducts **32**, **34**, and **36** (total yield 71%). The mixture of adducts was alkylated, affording compound **38** as a single diastereomer.



SCHEME 5. HMPA = hexamethylphosphoramide.

A similar imino Diels–Alder reaction between dihydro- $\beta$ -carboline **30** and diene **31** afforded three products (**33**, **35**, and **37**) (total yield 88%), which were directly alkylated to afford the 7-methoxyindoloquinolizidine derivative **39** as

a single product. Indoloquinolizidines **38** and **39** were treated separately with dimesyllithium, giving ketosulfoxides **40** and **41** as a mixture of diastereomers, respectively. The Pummerer reaction followed by intramolecular nucleophilic attack on the indole nucleus produced the aspidosperma derivatives **42** and **43**.



SCHEME 6

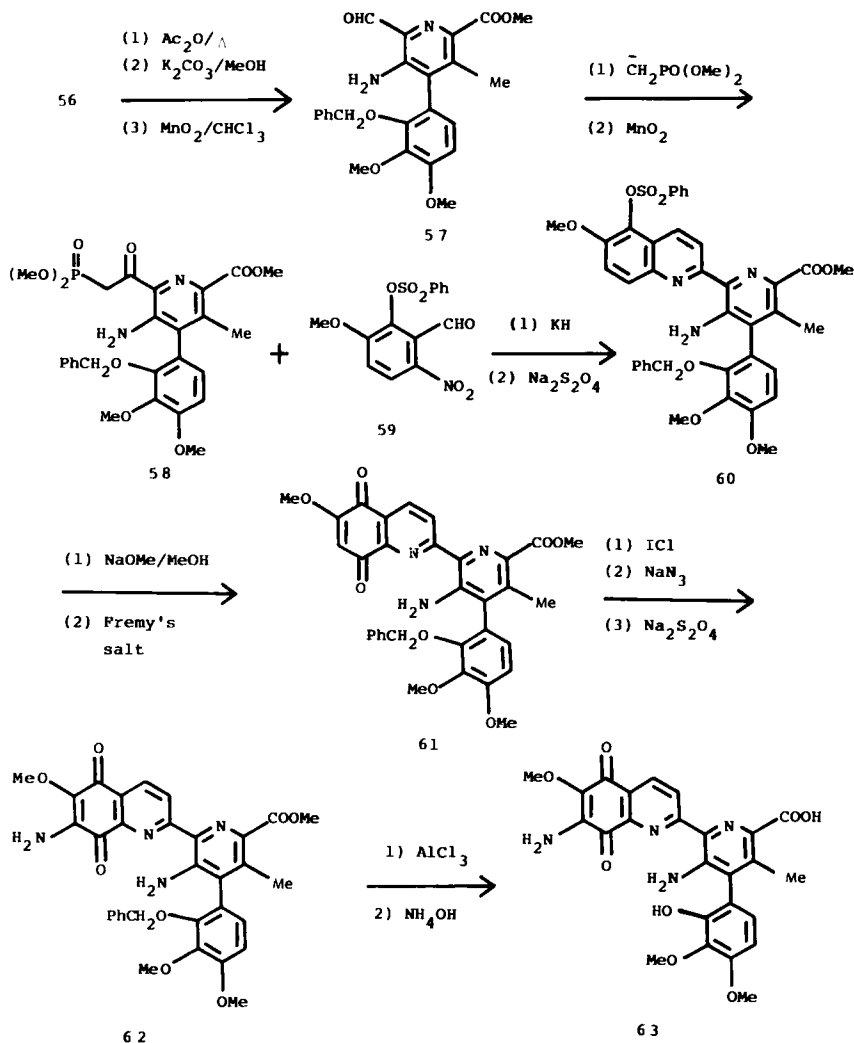
Reduction of the double bond of vinylogous lactams **42** and **43** with sodium cyanoborohydride and subsequent hydrogenolysis of the resulting thioethers gave rise to the pentacyclic ketones **44** and **45** as prepared by Büchi (71JA3299; 75JA6880). The conversions of the pentacyclic ketones to vindrosine (**46**) and vindoline (**47**) involved a five-step sequence (Scheme 5).

Weinreb and co-workers (80JA3962; 82JA536) completed the first total synthesis of the antitumor antibiotic streptonigrin in 1980. Their central strategy involved the use of an imino Diels–Alder reaction for the construction of the 4-phenylpyridine ring system (Scheme 6). The mixture of dienes **48** reacted with methoxyhydantoin **49** giving **50** as the major product, along with a regioisomer (together 56%). Without separation, the mixture of adducts was transformed in three steps to pyridine **51**. The pyridine **51** was oxidized with *m*-chloroperoxybenzoic acid (mCPBA) to the corresponding *N*-oxide, which underwent a Polonovsky rearrangement on heating in acetic anhydride to afford acetate **52**. This compound was converted to the quaternary salt **53**, which on treatment with cold potassium *t*-butoxide, followed by hydrolysis of the [2,3]-sigmatropic rearrangement product, afforded aldehyde **54**. *N*-Oxide acid **55** was then prepared from aldehyde **54**, and a modified Curtius rearrangement served to produce amine **56**.

The next sequence of steps was directed toward the attachment of this pyridine ring to a quinoline framework (Scheme 7). Amine **56** was transformed to  $\beta$ -ketophosphonate **58** in five steps via aldehyde **57**. Condensation of the anion derived from **58** with nitroaldehyde **59** gave chalcone, which on reductive cyclization yielded the tetracyclic system **60**. Cleavage of sulfonate **60** to the corresponding phenol, followed by a salt oxidation, led to quinone **61**. The amino group on the quinone ring was introduced by a three-step sequence, affording the aminoketone **62**. Cleavage of the benzyl group of **62** with aluminum chloride gave streptonigrin methyl ester, which was hydrolyzed with ammonium hydroxide to produce streptonigrin (**63**).

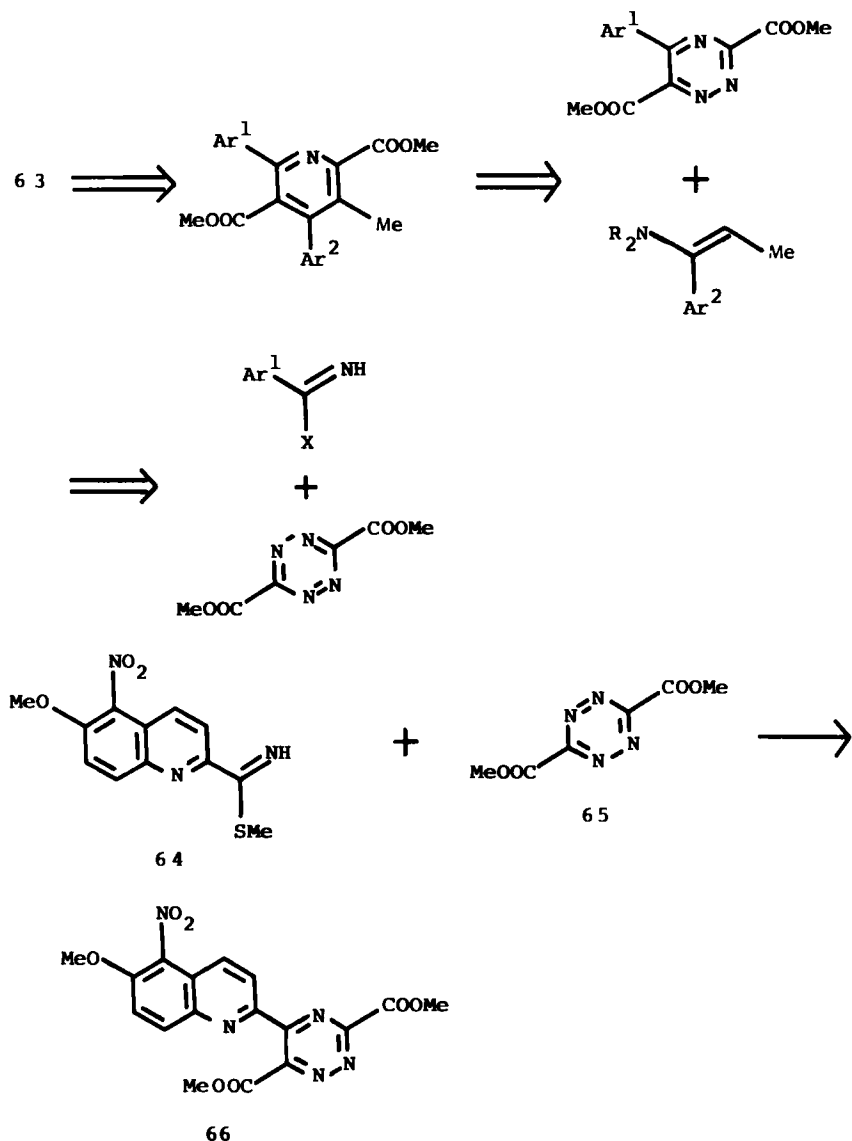
Boger and Panek (85JA5754) have also accomplished a formal total synthesis of streptonigrin (**63**) based on two hetero Diels–Alder reactions (Scheme 8). The initial cycloaddition of the *S*-methylthioimide **64** and 1,2,4,5-triazine-3,6-dicarboxylate **65** provided 1,2,4-triazine **66** (82%), which was then used as an azadiene component of the second Diels–Alder reaction. The following step will be described in Section III,B,1.

In 1974, Jagt and Van Leusen (74JOC564) found that sulfonyl cyanides are good dienophiles. At room temperature, tosyl cyanide (**67**) dissolved in cyclopentadiene **68** is converted into 3-tosyl-2-azabicyclo[2.2.1]hepta-2,5-diene (**69**) (95%). This is the first example of the formation of a primary Diels–Alder cycloadduct of a nitrile. Adduct **69** was hydrolyzed with acetic acid and water to the lactam **70**. Daluge and Vince (73JOC2311) used **70** to synthesize puromycin analog **76** (Scheme 9). Lactam **70** was hydrolyzed to the cis-amino



SCHEME 7

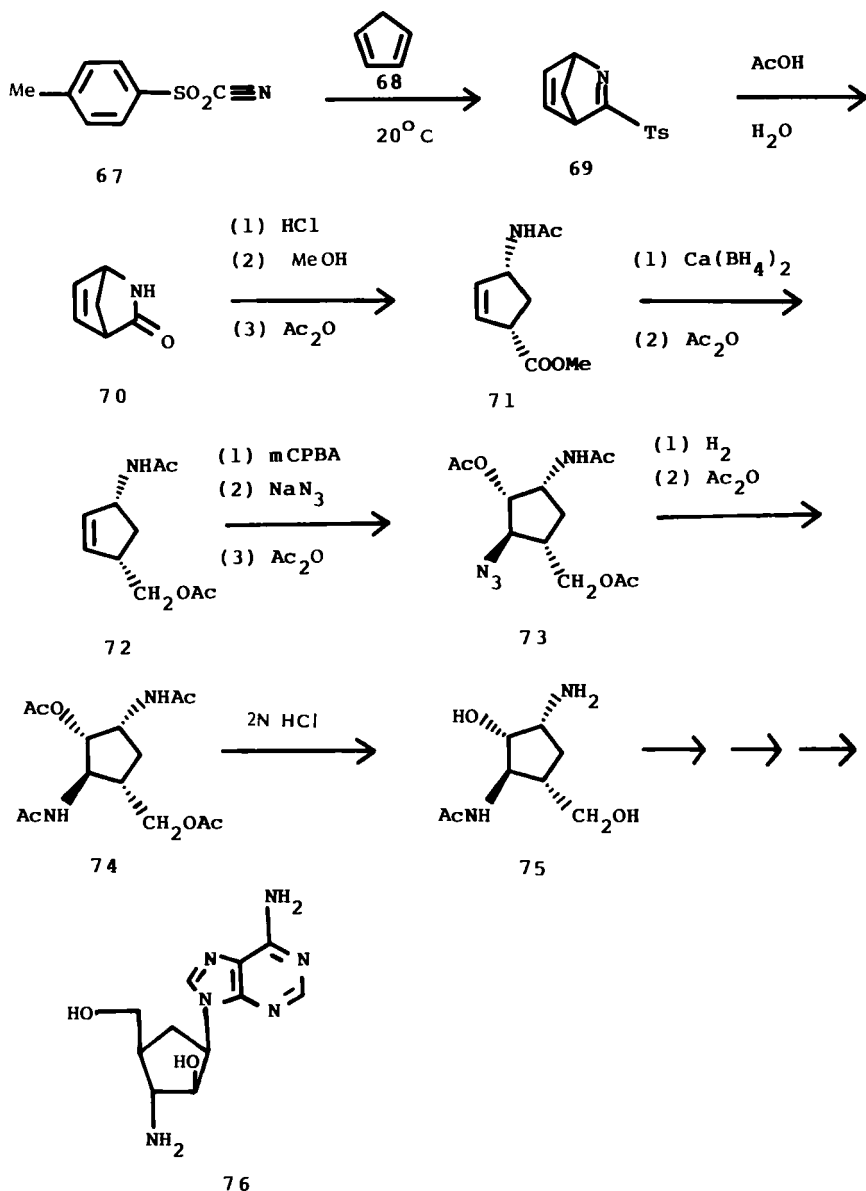
acid, which was esterified and acylated to give **71**. Reduction of the ester group was performed with calcium borohydride. After acetylation, amide ester **72** was obtained. Epoxidation of the double bond, followed by opening of the *cis*-epoxide by sodium azide, gave predominantly **73**. Catalytic hydrogenation of **73** followed by acetylation gave **74**. The tetraacetyl derivative (**74**) was selectively deacylated to **75** using acidic conditions. Condensation of amino alcohol **75** with 5-amino-4,6-dichloropyrimidine, ring closure with dideoxy-



SCHEME 8

methyl acetate, and then amination of the intermediate chloropurine gave puromycin analog 76 after deprotection.

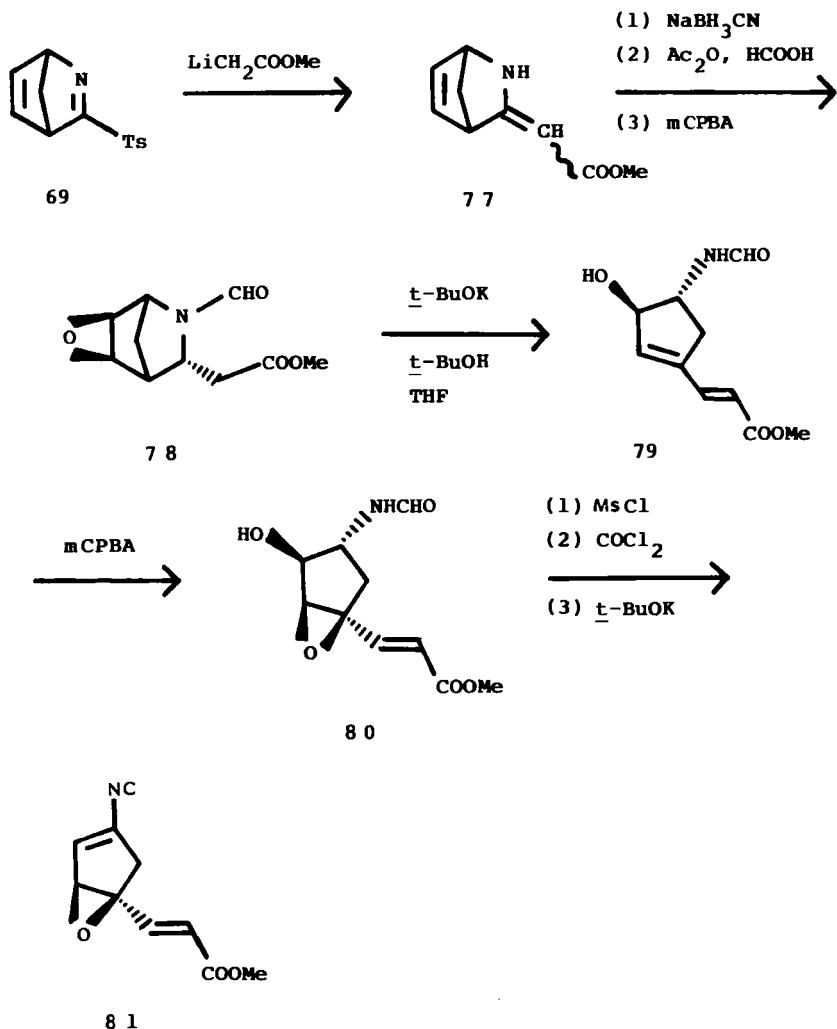
Fukuyama and Yung (81TL3759) used adduct **69** as a key starting material for the synthesis of methyl ( $\pm$ )-3-(3-cyano-6-oxabicyclo[3.1.0]hex-2-en-5-yl)-2-propenoate (**81**). The reaction of cycloadduct **69** with methyl lithioacetate gave unsaturated ester **77**. Reduction in acidic media of the conjugated double



SCHEME 9

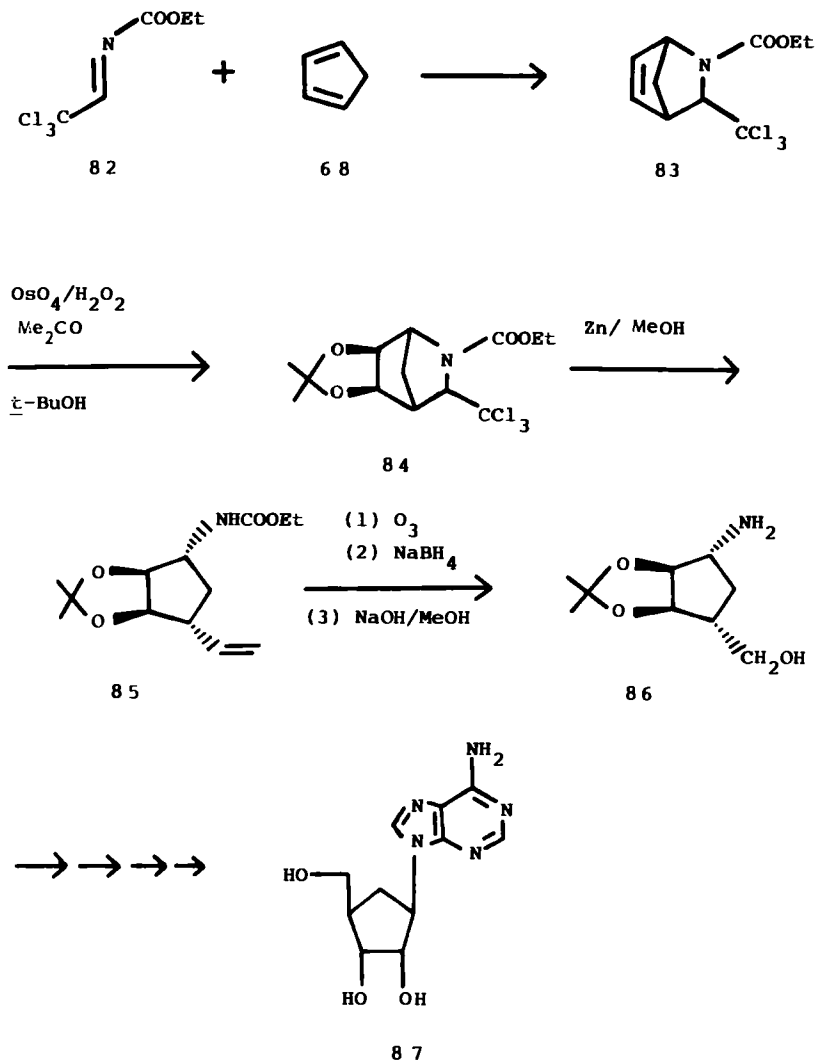
bond followed by N-formylation and epoxidation gave epoxide **78**. Treatment with a large excess of potassium *t*-butoxide caused ring opening to give cyclopentenol **79**. Further epoxidation of **79** with *m*-chloroperbenzoic acid gave epoxide **80**. Final transformation to natural product **81** involved hydroxyl elimination and elaboration of the cyanide moiety.





SCHEME 10

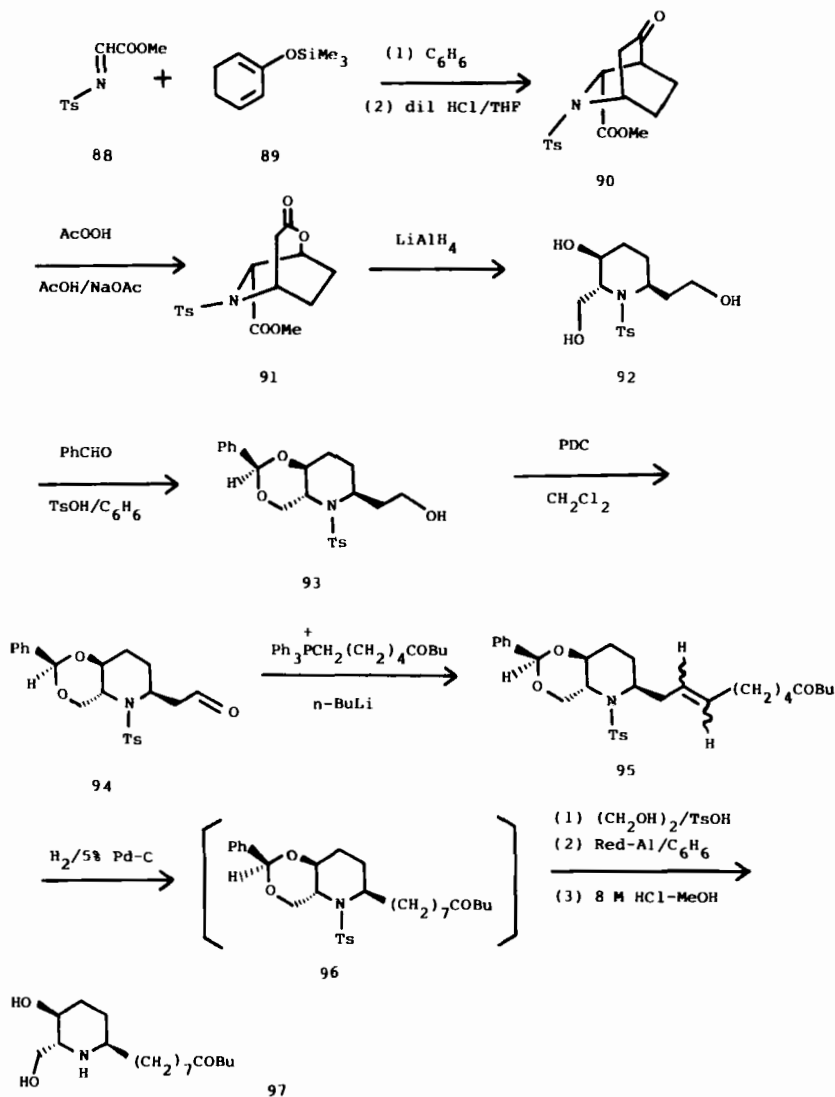
Saksena (80TL133) reported a short synthesis of antibiotic ( $\pm$ )-aristeromycin (**87**) by the use of cycloadduct **83** (73BCJ2922), which was prepared from the cycloaddition of imine **82** and diene **68** (Scheme 11). Catalytic osmylation in acetone of adduct **83** in a one-pot sequence gave the acetonide **84**. On refluxing with zinc powder in methanol, halogen-free olefin **85** was obtained. Ozonolysis of the double bond followed by reductive workup and deprotection of the amine gave amino alcohol **86**. By a standard four-step sequence (57JA5238), amino alcohol **86** was converted to aristeromycin (**87**).



SCHEME 11

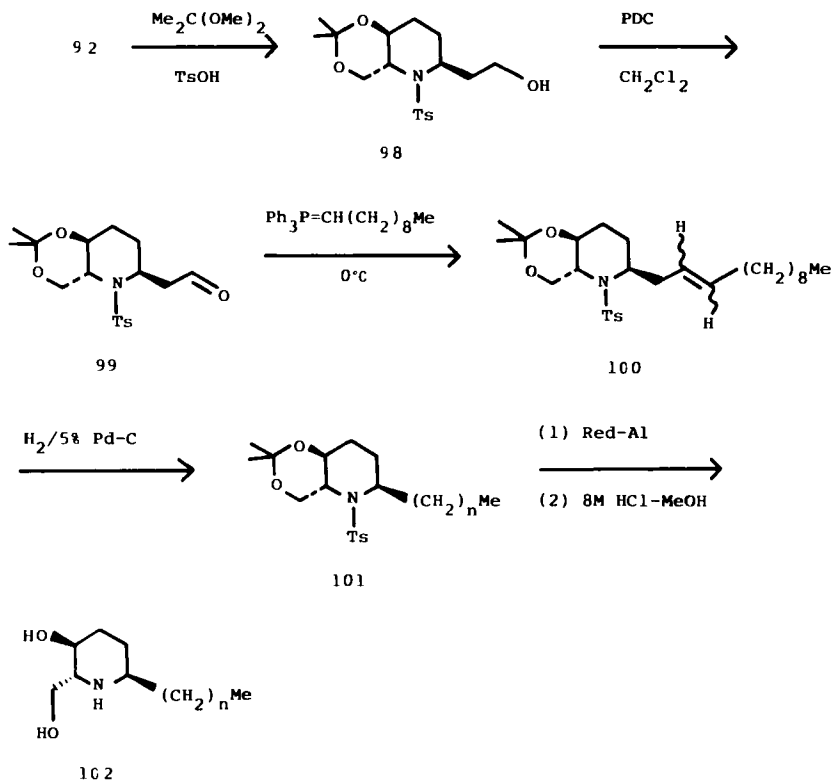
Holmes and co-workers (85CC37) have employed an imino Diels–Alder reaction for the construction of trisubstituted piperidine. The trisubstituted piperidine **92** (triol) is a useful precursor to all the naturally occurring prosopis piperidine alkaloids. Cycloaddition of imine **88** to silyloxyhexadiene **89**, followed by mild acid hydrolysis, gave the azabicyclooctanone **90** regio- and stereoselectively (83CC1490). Baeyer–Villiger oxidation of the bicyclic ketone **90** afforded bridgehead-migrated lactone **91**, which was reduced to triol **92** as

in Scheme 12. Conversion of the triol **92** into isoprosopinine B (**97**) went as follows. After protection of the triol with benzaldehyde and acid, the primary alcohol was oxidized by pyridinium dichromate (PDC) to the aldehyde **94**, which underwent a Wittig reaction to give the corresponding alkene (**95**) as a mixture of (*E*)- and (*Z*)-isomers. Hydrogenation, detosylation, and deprotection afforded isoprosopinine B (**97**).



SCHEME 12

Additionally, triol **92** was protected by dimethoxypropane to give the acetonide **98**. Oxidation of alcohol **98** by pyridinium dichromate gave the aldehyde **99**, which was subjected to a Wittig reaction to produce the alkene **100**. Hydrogenation of the double bond gave alkane **101**. Reductive cleavage of the tosyl group of **101**, followed by hydrolysis, afforded desoxyprosopinine **102** (Scheme 13).

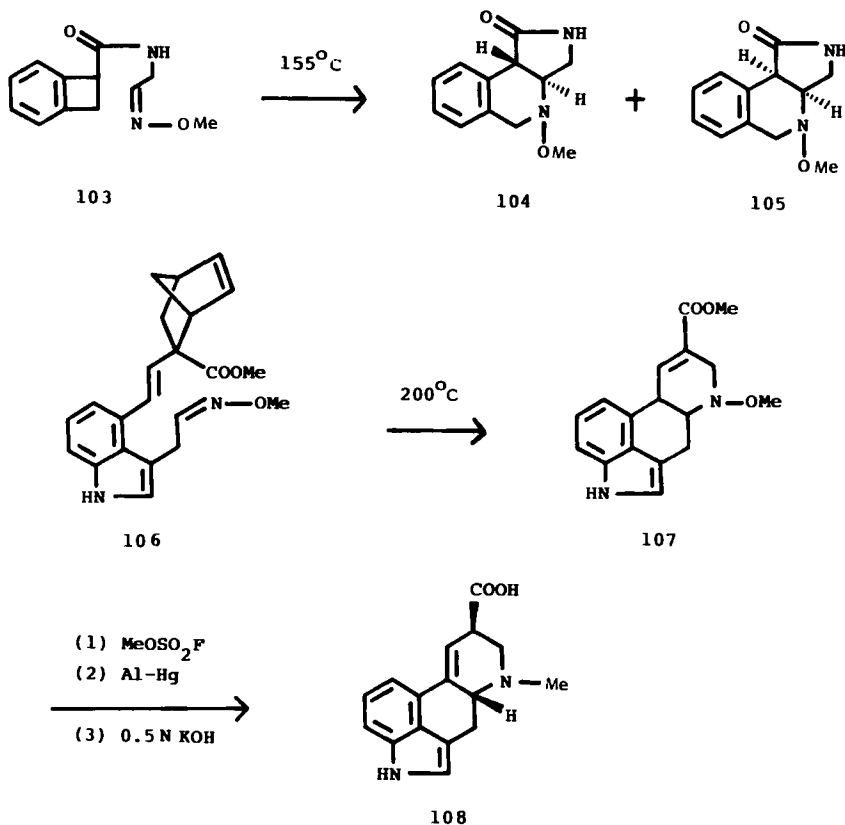


SCHEME 13

## 2. Intramolecular Cycloaddition Reactions

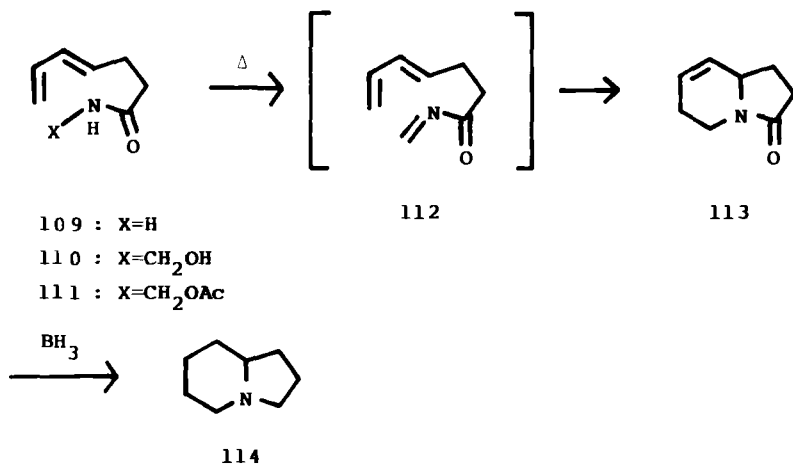
In 1971, one example of an intramolecular imino Diels–Alder reaction has appeared (71AG(E)1031). Oppolzer reported that a mixture of epimeric tricyclic lactams **104** and **105** is produced in good yield upon heating benzocyclobutene **103**. The Oppolzer group extended this methodology to a notable synthesis of ergot alkaloids, lysergic acid (**108**) (Scheme 14) (81HCA478). A dilute solution of imino ether having diene precursor **106** was

heated at 200°C in trichlorobenzene to afford a 67% yield of adduct **107** as a 3:2 mixture of epimers. This cycloaddition proceeds through an undetected diene oxime ether produced by a retro Diels–Alder reaction based on loss of cyclopentadiene. It is not clear whether the mixture of stereoisomers isolated from the cycloaddition results from epimerization of the  $\alpha,\beta$ -unsaturated ester under the reaction conditions or from a lack of stereoselectivity in the Diels–Alder reaction. This mixture was converted to racemic lysergic acid (**108**).



SCHEME 14

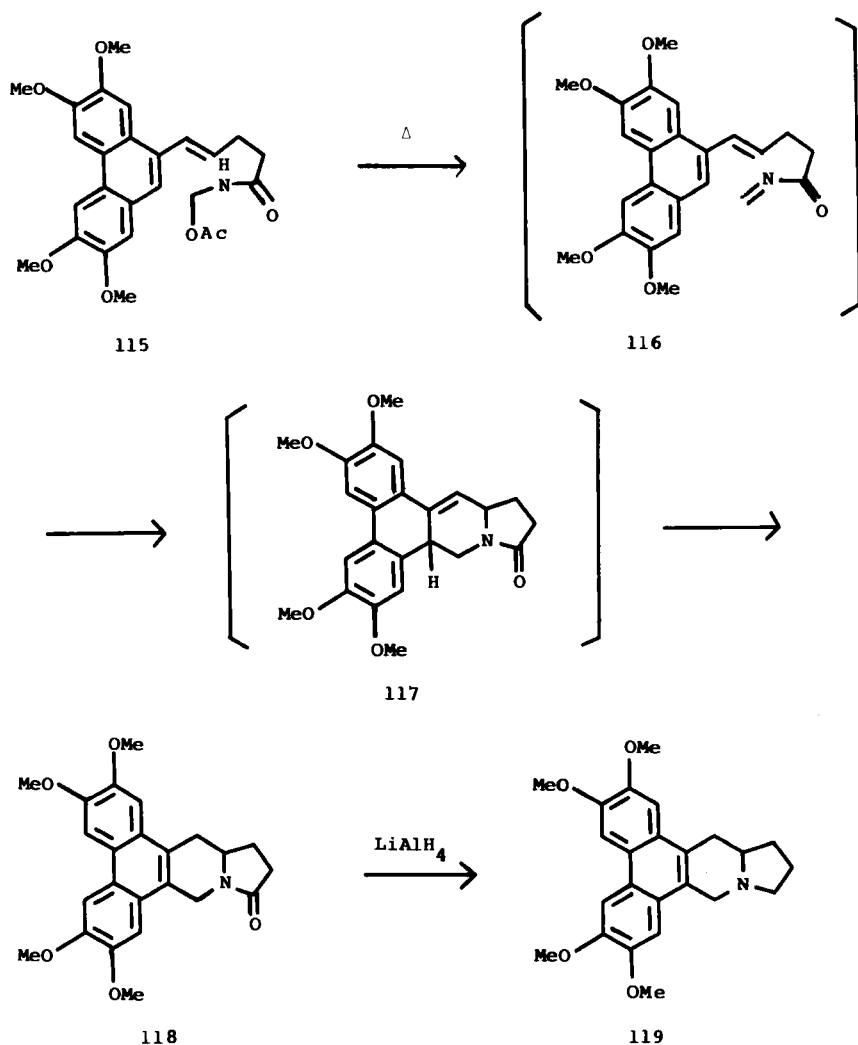
The Weinreb group (79H949; 82T3087; 85ACR16) found that *N*-acylimino compounds were the most attractive type of dienophile since they had been substantially studied in intramolecular processes. Although acyliminium dienophiles are most commonly generated from bisamide and biscarbamate under Lewis catalysis, they used neutral *N*-acylimines as a component of intramolecular Diels–Alder cycloaddition which might be generated from an asymmetrical precursor under mild conditions.



SCHEME 15

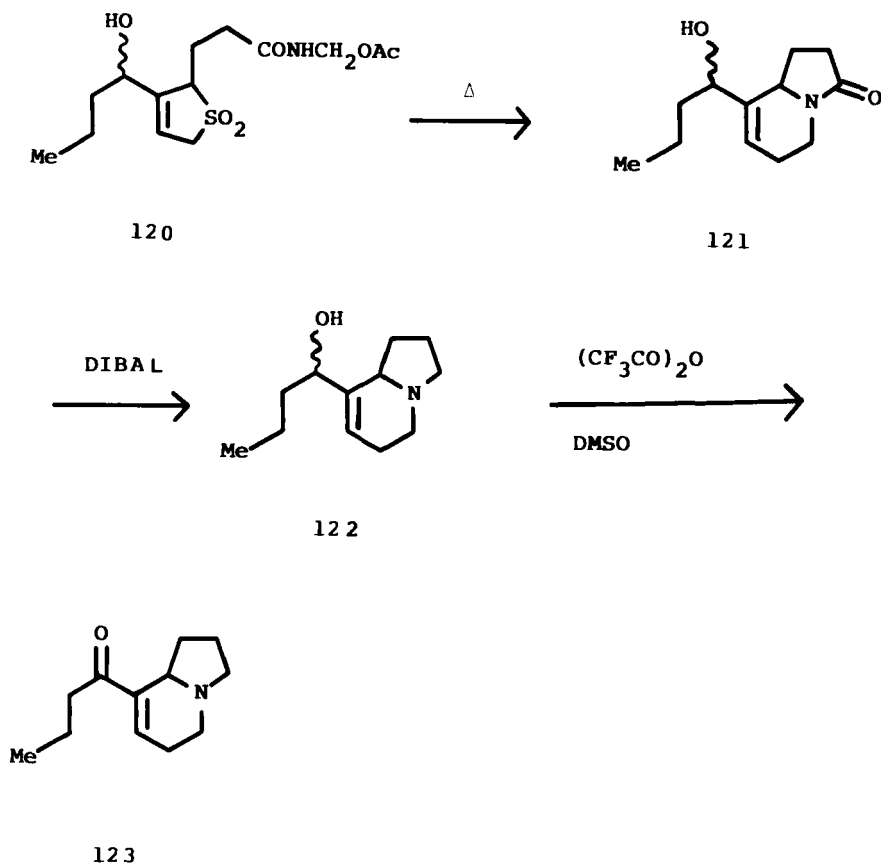
$\delta$ -Coniceine (**114**), the simplest indolizidine alkaloid, was synthesized as an initial target molecule by this methodology (Scheme 15) (79JA5073; 81JA6387). Amide diene **109** was converted to methylol **110** with aqueous formaldehyde and sodium hydroxide in glyme. The crude product was acetylated with acetic anhydride/pyridine to afford methylol acetate **111** in good yield. Pyrolysis of this acetate through a hot tube of glass helices yielded lactam **113** (73%) via the unstable *N*-acylimine intermediate (**112**) formed by elimination of acetic acid. Catalytic hydrogenation of the double bond of **113**, followed by lactam carbonyl reduction with diborane, afforded  $\delta$ -coniceine (**114**). The same group reported some applications in the area of indolizidine alkaloids. Tylophorine (**119**), a member of the phenanthroindolizidine alkaloid group, was chosen as the next target in order to establish whether an intramolecular imino Diels–Alder cycloaddition could be effected with a diene incorporated into an aromatic system (80JOC3372; 81JA6387). Methylol acetate **115**, prepared by a similar method, was heated as a dilute solution in bromobenzene at 220°C in a sealed tube to afford a 50% yield of the desired pentacyclic lactam (**118**) (Scheme 16). This transformation undoubtedly involves the *N*-acylimine **116**, which undergoes [4 + 2]-cycloaddition to **117**, followed by a 1,3-hydrogen shift to give the observed product. Reduction of lactam **118** with lithium aluminum hydride gave racemic tylophorine (**119**).

This methodology was further studied for the total synthesis of the *Elaeokarpus* alkaloids elaeokanine A (**123**) and B (**122**) (80JOC3372; 81JA6387). This monoene moiety was prepared in masked form via amide dihydrothiophene dioxide. After O-silylation of methylol acetate **120**, the



SCHEME 16

crude product in toluene was passed through a tube of glass helices at  $370^\circ\text{C}$  to give a 5:4 mixture of epimeric lactam alcohols **121** (68%). Reduction of the mixture with diisobutylaluminum hydride (DIBAL) afforded a difficult separable mixture of amino alcohols corresponding to elaeokanine B (**122**). Synthetic **122** was oxidized by the Swern method (76JOC3329) to give elaeokanine A (**123**).

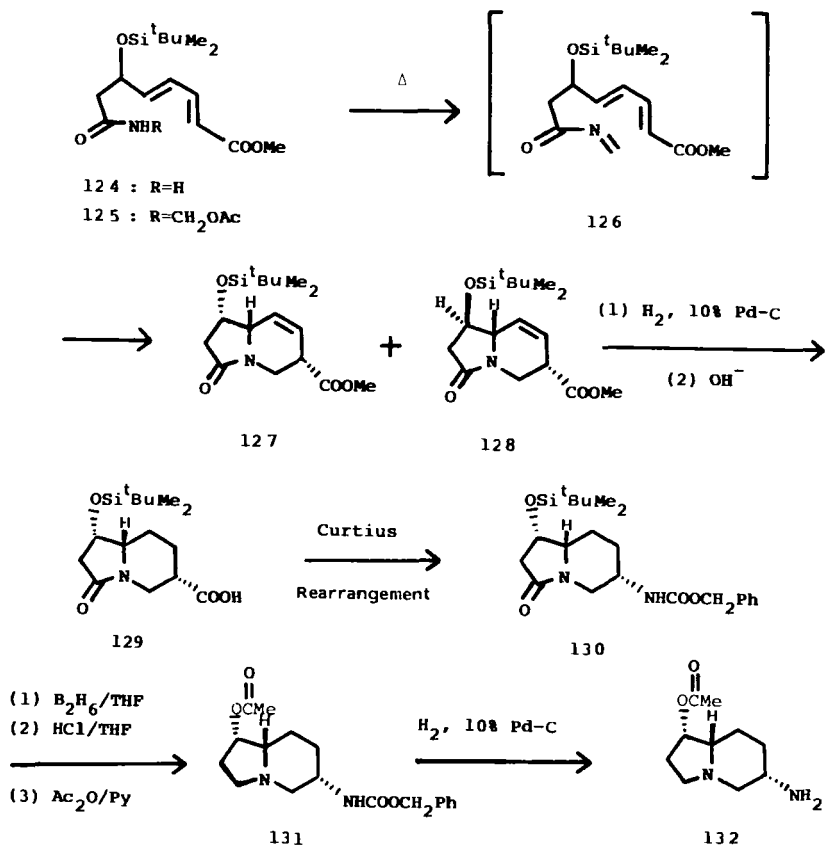


SCHEME 17

As a final test of the synthetic strategy in the indolizidine alkaloid field, Weinreb turned to the fungal neurotoxin slaflamine (**132**) (82JA7065). Methylol acetate **125** was prepared in several steps from amide **124**. When methylol acetate **125** was heated in refluxing *o*-dichlorobenzene, a separable 1:1.8 mixture of epimeric Diels–Alder adducts **127** and **128** (82%) was obtained via the *N*-acylimine intermediate **126**. Catalytic hydrogenation of adduct **127**, followed by basic hydrolysis, produced acid lactam **129**. Curtius rearrangement of this compound led to carbamate lactam **131** (70JA7615) and to racemic slaflamine (**132**) (Scheme 18).

Weinreb's group has developed a stereoselective approach to a quinolizidine alkaloid *epi*-lupinine **139**, which uses this methodology to construct efficiently the necessary bicyclic 6/6 ring system and to establish the proper

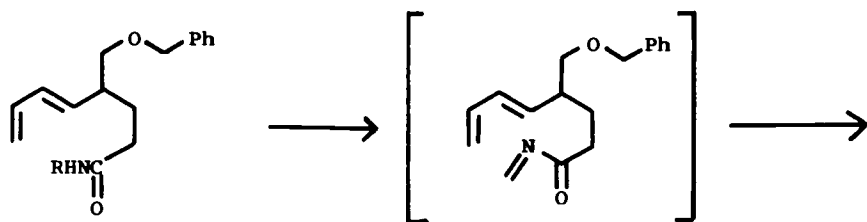




SCHEME 18

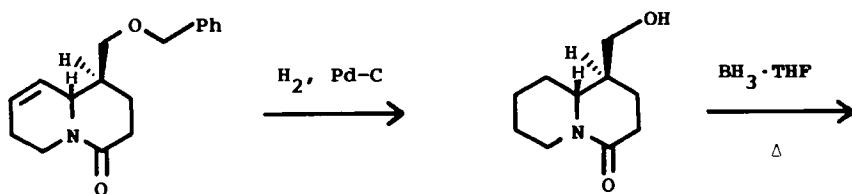
relative stereochemistry (Scheme 19) (83JOC3661; 83TL261). Amide **133** was transformed to its methylol acetate (**135**) using paraformaldehyde with a catalytic amount of cesium carbonate and acylation. Upon heating in refluxing *o*-dichlorobenzene, acetate **135** clearly cyclized to afford a single bicyclic lactam **137**, which was converted into *epi*-lupinine **139** in two steps. The stereochemistry was assigned as in **137**, and it was demonstrated that the transition state (**140**) in the six-membered lactam ring (quasi boat) would lead to this stereochemistry.

Recently, lupinine **4** and *epi*-lupinine **139** were also synthesized by Takayama's group (85H2913) based on an intramolecular imino Diels–Alder reaction (Scheme 20). Thermolysis of acetate **141** in toluene containing sodium hydrogen carbonate in a sealed tube at 200°C for 2 hr gave lactam **143** in 80% yield via desulfonylation and subsequent intramolecular cycloaddition of **142**.



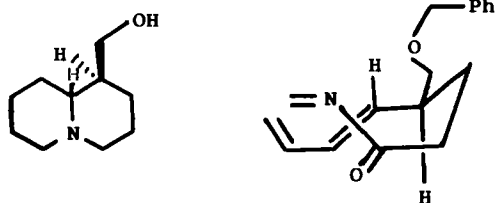
133 : R=H

136

134 : R=CH<sub>2</sub>OH135 : R=CH<sub>2</sub>OAc

137

138



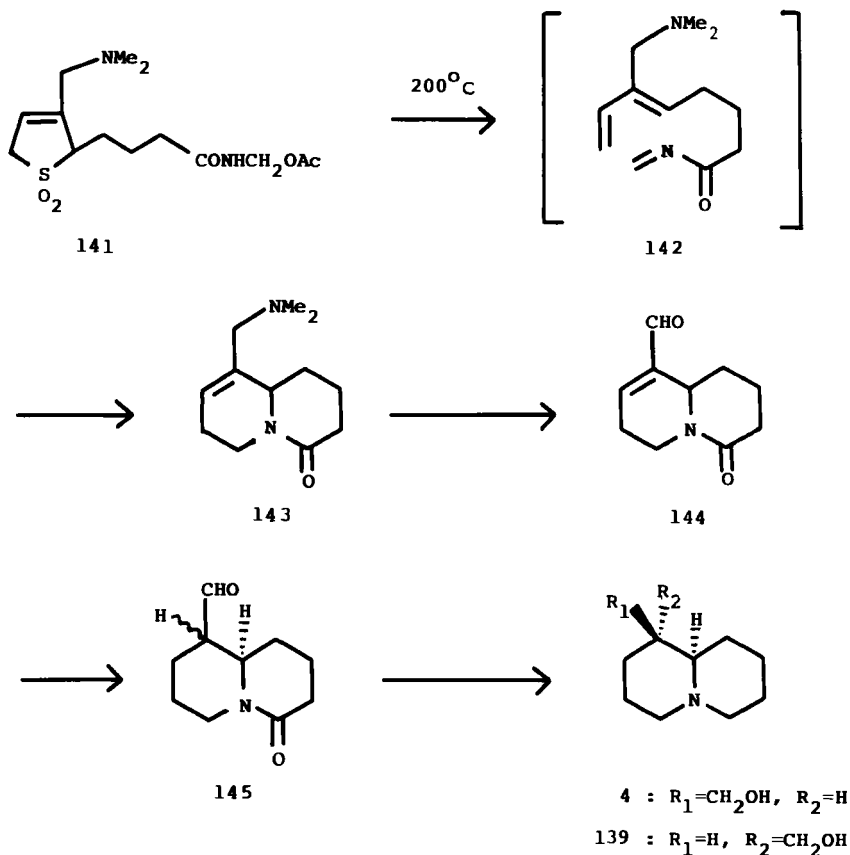
139

140

SCHEME 19

The lactam **143** was treated with *m*-chloroperbenzoic acid, followed by treatment with acid anhydride to yield the aldehyde **144**. Catalytic hydrogenation of unsaturated aldehyde **144** gave saturated aldehyde **145**, and reduction of **145** with lithium aluminum hydride provided racemic lupinine **4** and racemic epilupinine **139**.

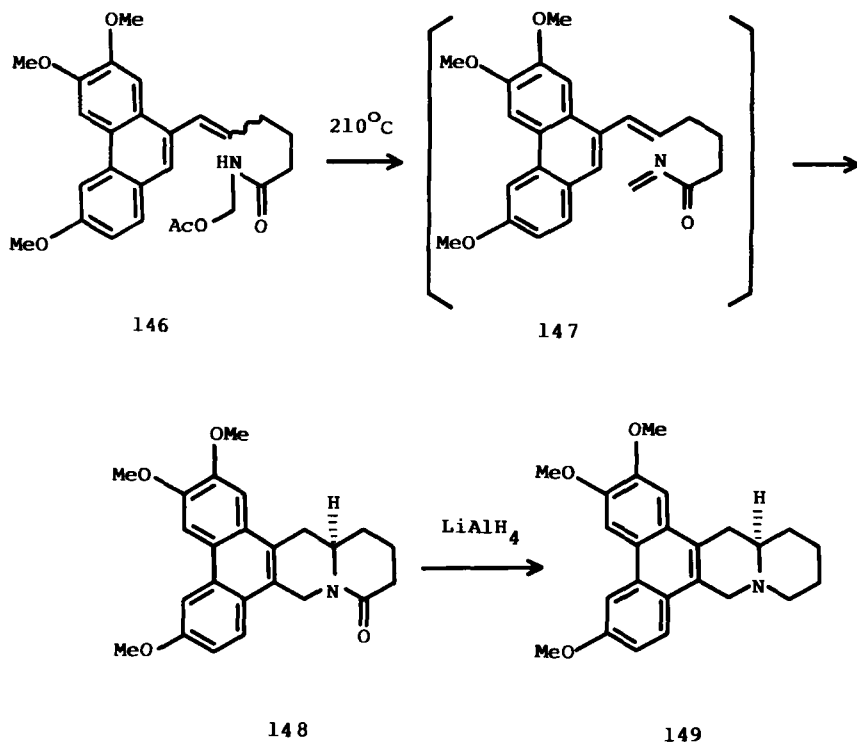
The phenanthroquinolizidine alkaloid cryptopleurine (**149**), which is a homologue of tyrophorine (**119**), was synthesized by the Weinreb group via the methylol acetate derivative (**146**) of an inseparable mixture of (*E*)- and (*Z*)-



SCHEME 20

isomers. Heating this mixture at  $210^{\circ}\text{C}$  in *o*-dichlorobenzene gave a 66% yield of lactam **148** and 30% of the uncyclized primary amide derived from the (*Z*)-isomer of **146**. Reduction of **148** with lithium aluminum hydride yielded racemic cryptopleurine (**149**) (Scheme 21).

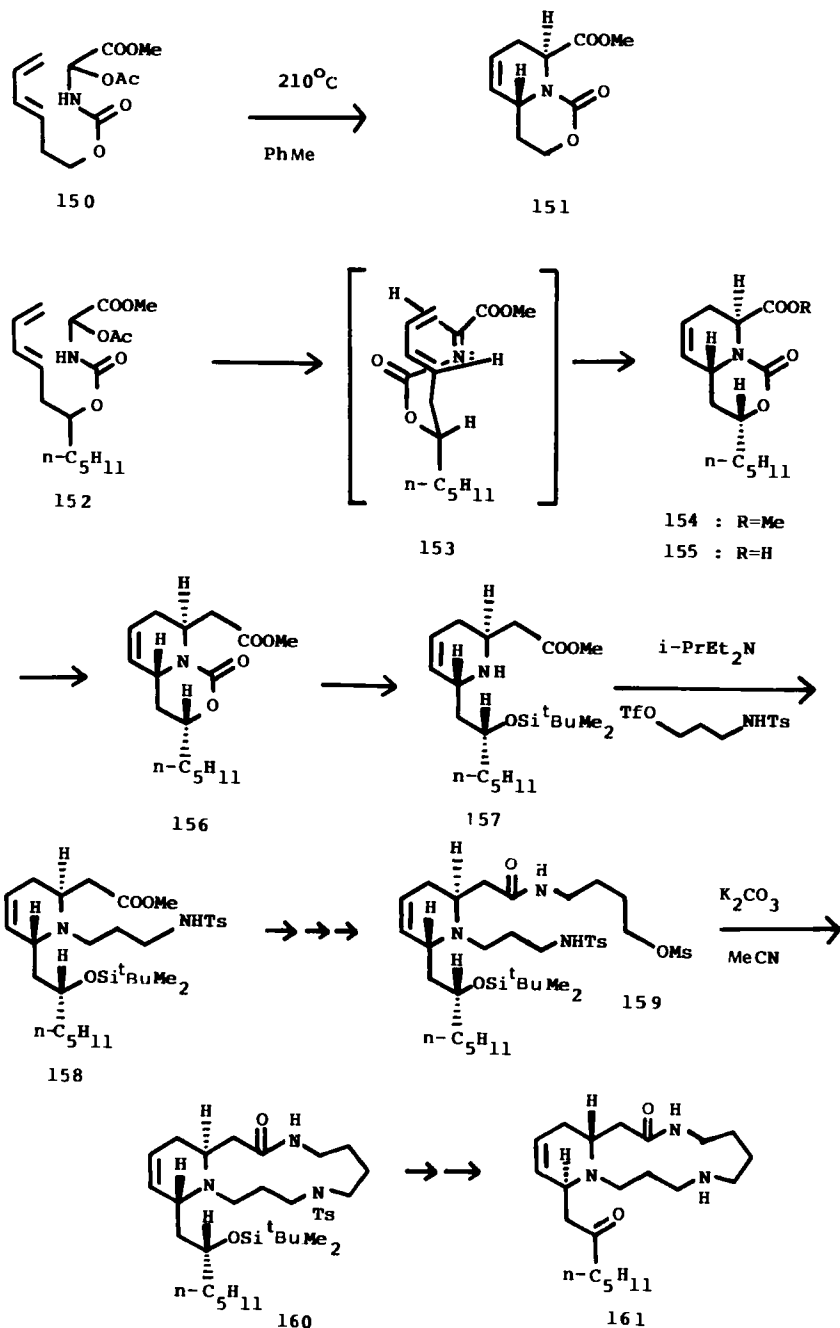
Finally, one of the major objectives in this field is the synthesis of the macrocyclic spermidine-derived alkaloid anhydrocannabisativene (**161**). In the model series, methylol acetate **150** was synthesized by the use of methyl glyoxylate, followed by acetylation of the methylol. Heating this compound produced only one adduct, which was shown to have structure **151** by X-ray crystallography on the corresponding carboxylic acid. This product has the cannabisativene oxygenation pattern and trans stereochemistry (Scheme 22) (80JA1153; 81JA7573; 84JA3240). Pyrolysis of methylol acetate **152** at  $215^{\circ}\text{C}$  in toluene afforded an 83% yield of a single bicyclic adduct **154**, whose



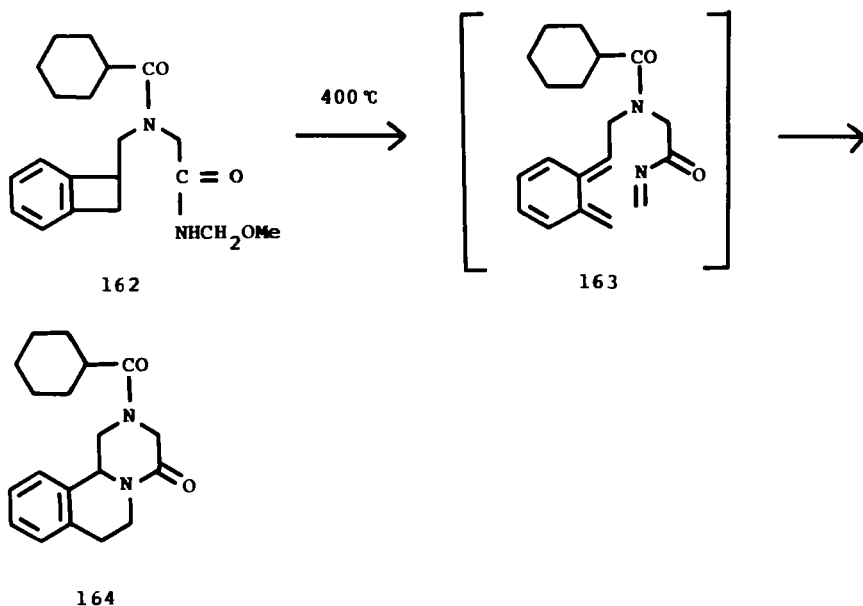
SCHEME 21

structure was confirmed by X-ray crystallography of the acid. This cyclization occurs through an (*E*)-acylimine having the *N*-acyl group endo in the transition state. A conformation like **153** would predominate. For the synthesis of anhydrocannabisativene, the carboxylic acid **155** was converted by an Arndt–Eistert reaction to **156**, which was converted to amino ester **157** using triflate through ring opening of **156**. This compound was transformed in three steps to mesylate **159**, which upon treatment with potassium carbonate under high dilution yielded the 13-membered lactam **160**. Removal of the *N*-tosyl group of **160** was effected with sodium in ammonia, after which the *O*-silyl group was cleaved and the resulting alcohol oxidized to racemic cannabisativene **161**.

The Berkovitz group achieved the synthesis of praziquantel (**164**) (used to treat schistosomiasis) through an intramolecular imino Diels–Alder route (84JOC5269). They failed in the initial reaction using the methylol acetate. However, the less labile methoxy group of **162** worked reasonably well as a leaving group. Pyrolysis of precursor **162** in various solvents was unsuccessful, but succeeded in the gas phase (49%) (Scheme 23).

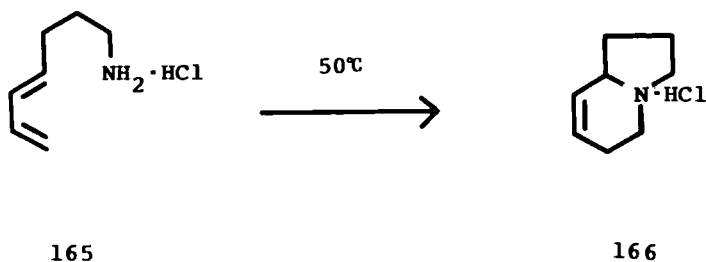


SCHEME 22; Tf = triflate.



SCHEME 23

Recently, Larsen and Glieco (85JA1768) reported that simple unactivated iminium salts, generated *in situ* under Mannich-like conditions, react with dienes in an exceptionally mild and convenient aqueous inter- and intramolecular Diels–Alder reaction (Scheme 24). Treatment of (*E*)-4,6-heptadienylamine hydrochloride (165) with 37% aqueous formaldehyde at  $50^\circ\text{C}$  for 48 hr gave a 95% yield of crystalline dehydro- $\delta$ -coniceine (166). This intramolecular iminium Diels–Alder strategy offers a mild and highly practical alternative to pyrolysis. Moreover, they examined the generality of this methodology to construct the necessary bicyclic 6/6 ring system of a number of alkaloids.



SCHEME 24

## B. C=O DIENOPHILES

### 1. Intermolecular Cycloaddition Reactions

Certain types of carbonyl compounds are capable of acting as dienophiles in [4 + 2]-cycloadditions. Generally only very electrophilic carbonyl groups are highly reactive. Recent and initial use of C=O dienophiles in Diels–Alder reactions have been summarized in excellent reviews (82T3087; 84MI1).

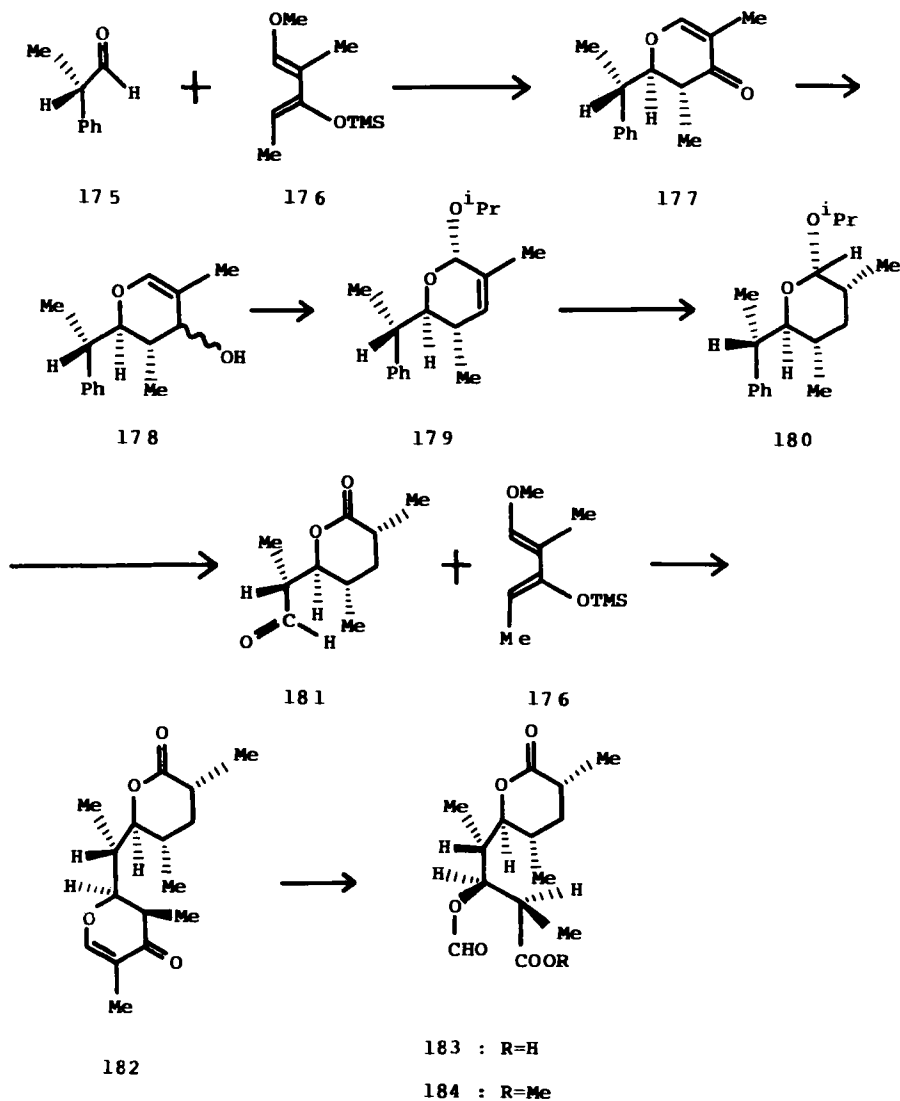
Danishesky discovered that highly oxygenated 1,3-dienes react with various types of aldehyde under Lewis acid catalysis to afford  $\gamma$ -pyrones possibly derived from Diels–Alder adducts (78TL1982). Recently, he reported many elegant applications of this methodology to natural product syntheses. The siloxydiene **167** reacted with benzyloxyacetaldehyde **168** to afford adduct **169**, which was subsequently converted to talose derivative **170** (82JA358). The diene **171** underwent cycloaddition with the chiral aldehyde **172** under various conditions to yield pyrone **173** and its C-4 epimer. Pyrone **173** was efficiently converted to the Prelog–Djerassi lactone **174** (Scheme 25) (82JA360; 82JOC1981; 84JA2456; 85JOC4650).

A synthesis of the C<sub>1</sub>–C<sub>9</sub> fragment of 6a-deoxyerythranolide B aglycon (**184**) was achieved utilizing this methodology (85JA1246). Reaction of aldehyde **175** with diene **176** in methylene chloride at –78°C under the influence of boron trifluoride etherate followed by treatment with trifluoroacetic acid in tetrahydrofuran afforded a diastereomeric mixture of adducts **177** (95%). Treatment of major component **177** with diisobutylaluminum hydride in toluene afforded a mixture of epimers **178**, which was treated with isopropyl alcohol and *p*-toluenesulfonic acid to produce isopropyl glycoside **179**. Reduction of **179** through the action of hydrogen over palladium aluminum catalyst gave the dihydro product **180**. Treatment of **180** with ozone in aqueous acetic acid containing a trace of trifluoroacetic acid followed by oxidative workup with hydrogen peroxide afforded the Prelog–Djerassi lactone aldehyde **181**. The aldehyde **181** was again subjected to the action of diene **176** in the presence of zinc chloride. A major product formulated as **182** by X-ray crystallography was obtained in 43% yield. In the final step, **182** was subjected to ozonolysis followed by oxidation with hydrogen peroxide to afford formate acid **183**. This compound was converted to the formate methyl ester **184** corresponding to the C<sub>1</sub>–C<sub>9</sub> fragment of the Masamune synthesis (81JA1568).

Danishesky investigated the synthesis of the *exo*-brevicommin **190**, mouse androgen **193**, and carbon-linked disaccharide **196** by the use of 1,3-dioxygenated butadienes and chiral aldehydes under Lewis acid catalysis (84JA2455; 85JA1256). The cyclocondensation of diene **185** in the presence of magnesium bromide gave only adduct **187** in 76–80% yield. High stereo-



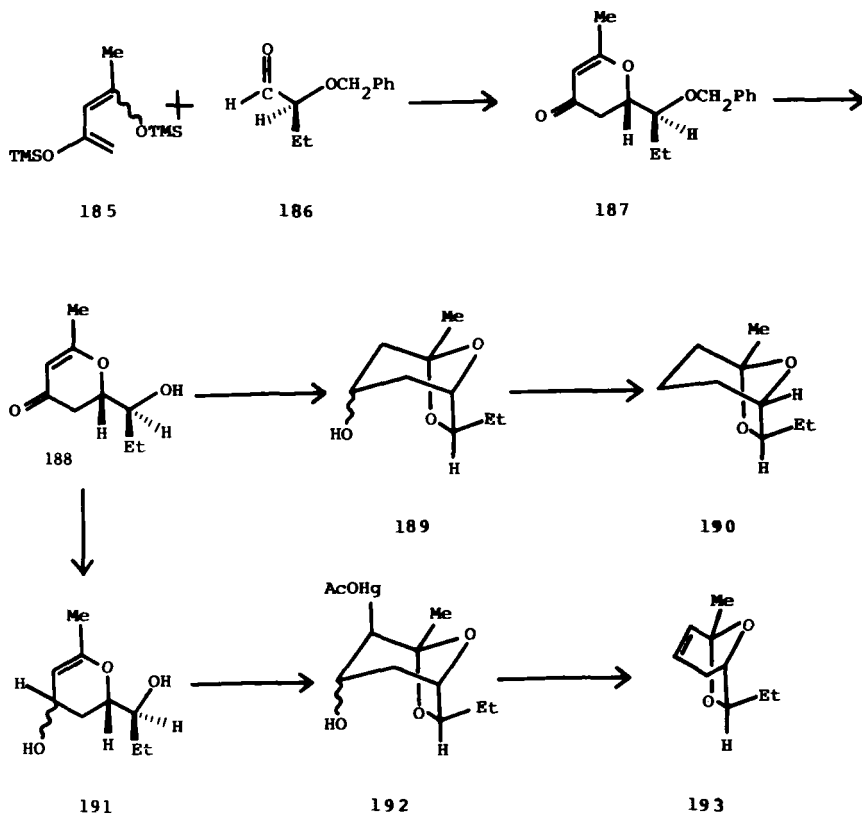




SCHEME 26

selectivity had been achieved. Reaction of adduct **187** with boron trifluoride etherate/dimethyl sulfide led to a high yield of debenzylated product **188**. The oxymercuration with mercuric acetate of **188** gave an  $\alpha$ -mercurio ketone. Upon reduction with sodium borohydride, the presumed mercurio ketone gave rise to alcohol epimers **189**. Reaction of **189** with bis-(dimethylamino)phosphorochloridate followed by reduction of the result-

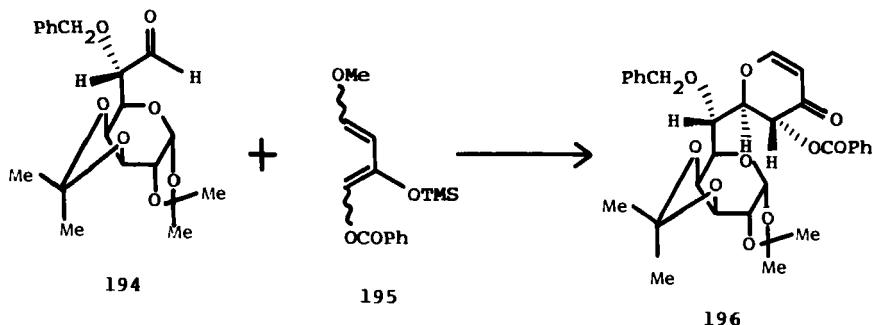
ant phosphoramidate with lithium in ethylamine gave *exo*-brevicommin (**190**) in 50% overall yield. The adduct **187** has been further utilized in the synthesis of mouse androgen **193**. Reduction of ketone **188** with diisobutyl aluminum hydride afforded the glycol **191**. Treatment of this compound with mercuric acetate in tetrahydrofuran gave the mercuriocarbinol **192**, which was converted to androgen **193** by retro oxymercuration with methanesulfonyl chloride (Scheme 27).



SCHEME 27

Furthermore, the chelation-controlled facially selective cyclocondensation of chiral alkoxy aldehyde **194** with diene mixture **195** in the presence of magnesium bromide in benzene gave the carbon-linked disaccharide (**196**) as a single product in 79% yield (Scheme 28).

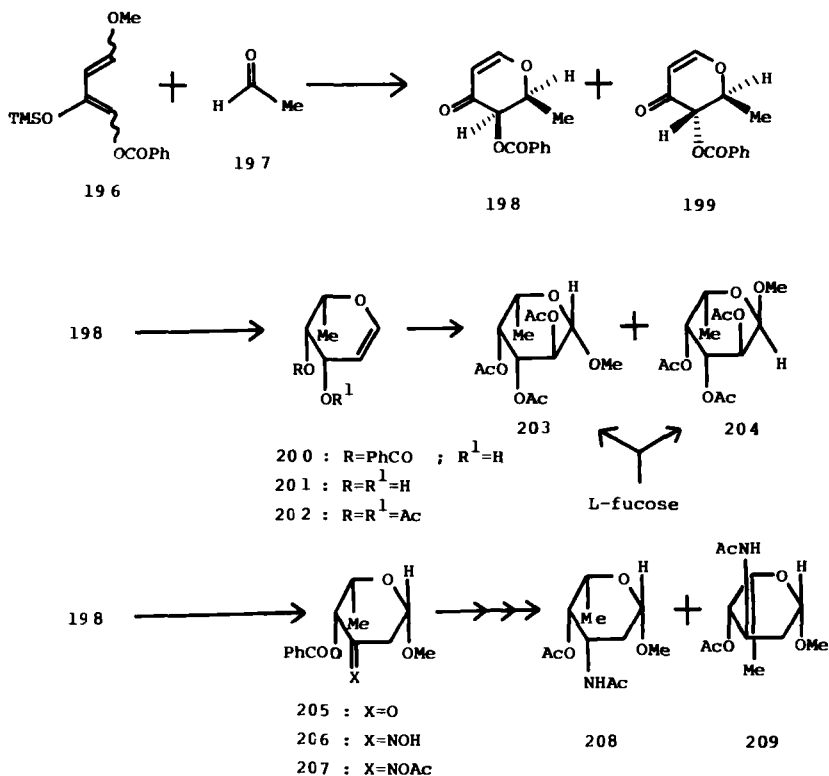
Danishefsky has extended this methodology for the synthesis of ( $\pm$ )-fucose and ( $\pm$ )-daunosamine (85JA1269). Reaction of silyloxydiene **195** with acetaldehyde (**197**) in the presence of anhydrous zinc chloride gave 90% of a 3.3:1



SCHEME 28

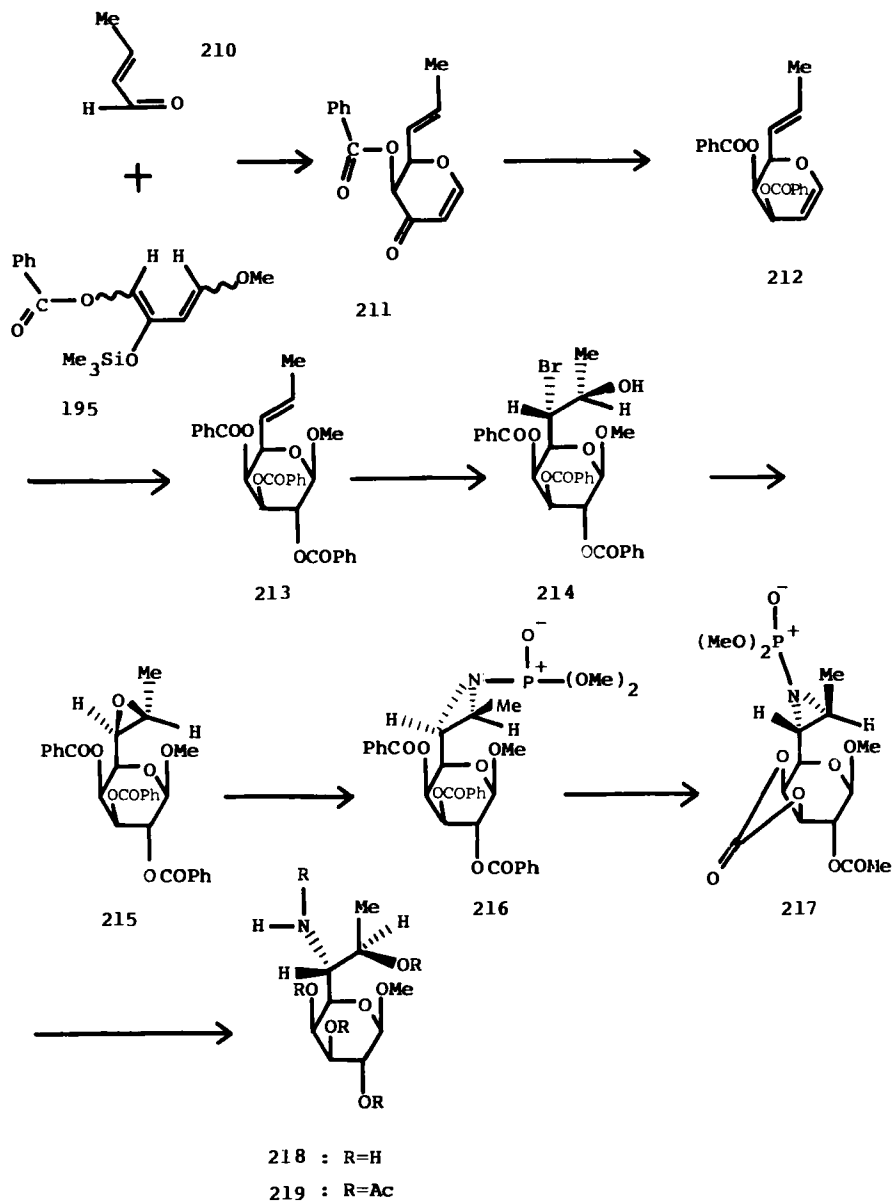
mixture of dihydropyrones **198** and **199** (4:1 in the case of  $\text{BF}_3 \cdot \text{OEt}_2$ , 70%). Reduction of the separable isomer **198** with sodium borohydride/cerous chloride gave fucal derivative **200**. Treatment of **200** with potassium carbonate afforded fucal **201**. Upon acetylation of **201** with acetic anhydride, the acetate **202** was obtained. Reaction with *m*-chloroperbenzoic acid followed by acetylation afforded an anomeric, separable mixture of the methyl fucosides **203** and **204** (2:1). These compounds were identical with the authentic  $\beta$ - and  $\alpha$ -methylfucoside derived from L-fucose (Scheme 29). The dihydropyrone **198** also provided a convenient entry to the ( $\pm$ )-daunosamine series. Reaction of **198** with mercuric acetate afforded a mercurial ketone, which, upon reduction with sodium cyanoborohydride, gave the  $\beta$ -methoxy ketone **205**. Compound **205** reacted with hydroxylamine to give oxime **206**. After acetylation, treatment of the mixtures with borane-THF produced the desired 3-amino system. After cleavage of the benzoate and acetyl group, a 2:1 ratio of two compounds was obtained. The major compound (50–55%) was the methyl-( $\pm$ )-3,4-diacetyl-daunosamine **208**. The minor diacetate derived from **207** through the borane-THF reduction sequence was the ( $\pm$ )-3-epidaunosamine derivative **209** (Scheme 29).

In the course of their application to the natural product, Danishefsky provided a total synthesis of ( $\pm$ )-lincosamine (Scheme 30) (83JA6715; 85JA1274). An intermolecular hetero Diels-Alder reaction of the diene mixture **195** with crotonaldehyde (**210**) under the influence of trifluoroacetic acid at  $-78^\circ\text{C}$  gave a 67% yield of the 2-[(*E*)-1-propenyl]pyrone **211**. Reduction of the ketone **211** by Luche's procedure (79JA5848) followed by benzylation afforded the galactal derivative **212**. Treatment of **212** with *m*-chloroperbenzoic acid in anhydrous methanol followed by benzylation afforded the methyl galactoside **213**. Reaction of **213** with N-bromosuccinimide in the presence of wet acetic acid produced a single bromohydrin (**214**).



SCHEME 29

Treatment of **214** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) gave epoxide **215**, which on reacting with tetra-*n*-butylammonium azide in the presence of trimethylsilyl azide gave a high yield of azidoalcohol silyl ether. The azidoalcohol obtained upon desilylation was converted to the *N*-(dimethylphosphoryl)aziridine **216** in a two-step sequence. Hydrolysis of the benzoyl group gave the triol. The C-3 and C-4 hydroxyl groups of the triol were converted to a cyclic carbonate by carbonyldiimidazole. The C-2 hydroxyl group simultaneously was converted to a mixed imidazole, which was treated with methanol to give compound **217**. Reaction of **217** with hot glacial acetic acid afforded phosphoramidate. Treatment of the solvolysis product with potassium carbonate/methanol cleaved all the blocking groups to produce  $\beta$ -methylincosaminide **218**. Acetylation of **218** led to its pentaacetate **219**; this synthesis of lincosamine is highly stereoselective in its introduction of six contiguous centers (C-2–C-7).

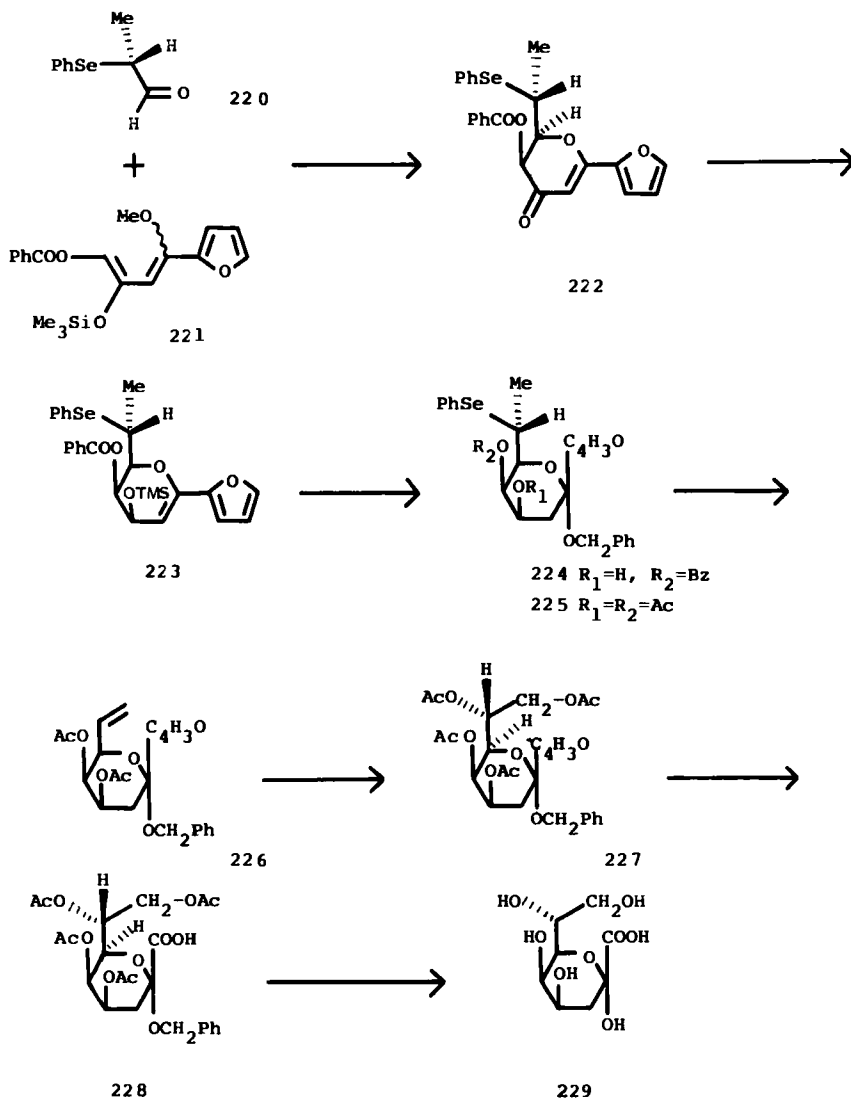


SCHEME 30

A Diels–Alder reaction of a C=O dienophile with a diene has also been used in the total synthesis of 3-deoxy-D-manno-2-octulopyranosate (KDO) (**229**) (Scheme 21) (85JA1280). The reaction of phenyl seleno aldehyde **220** with diene **221** was carried out in ether at  $-78^{\circ}\text{C}$  under  $\text{BF}_3$  catalysis. Treatment of the product with trifluoroacetic acid afforded a 58% yield of the *cis* dihydropyrone derivative **222**, along with the separable *trans* isomer (24%). Reduction of the pyrone **222** with sodium borohydride in the presence of ceric chloride provided the alcohol, which was protected as its trimethylsilyl ether **223**. Reaction of **223** with benzyl alcohol in the presence of camphorsulfonic acid (CSA) produced a single glycoside (**224**), in which the silyl ether group has been removed. The benzoyl group was cleaved by potassium carbonate to afford a diol, which on acetylation gave rise to a diacetate (**225**). Oxidative deselenation of **225** with aqueous hydrogen peroxide gave the vinyl compound **226**, which was treated with osmium tetroxide followed by acetylation to afford tetraacetate **227**. Cleavage of the furan ring by ruthenium tetroxide produced the acid **228**. Finally, methanolysis of the acetate and hydrogenolysis of the benzyl group of **228** produced synthetic ( $\pm$ )-KDO (**229**).

Two homo Diels–Alder reactions and a hetero Diels–Alder reaction, each using a silyloxydiene, have been used in a total synthesis of vinemycinone B<sub>2</sub> methyl ester (**236**) by Danishefsky (84JA2453; 85JA1285). Ketoaldehyde **231**, prepared by two Diels–Alder cycloadditions, reacted with diene **230** in chloroform in the presence of  $\text{Eu}(\text{fod})_3$  to produce the silyl enol ether **232** having a *cis* relationship between the methyl and aromatic residues (90–95%). Treatment of adduct **232** with borane dimethyl sulfide followed by oxidative workup with aqueous hydrogen peroxide afforded the alcohol **233** (*anti* to the methyl and aryl group). Demethylation of **233** with boron tribromide yielded the phenol **234**. Addition of the Grignard reagent derived from (–)-methyl acetate to ketone **234** afforded the alcohol **235**, along with its antipode. The product was separated by high-pressure liquid chromatography (HPLC) into pure components. One was vineomycinone B<sub>2</sub> (–)-mentyl ester; subsequent transesterification with potassium carbonate in methanol afforded the vineomycinone B<sub>2</sub> methyl ester **236**.

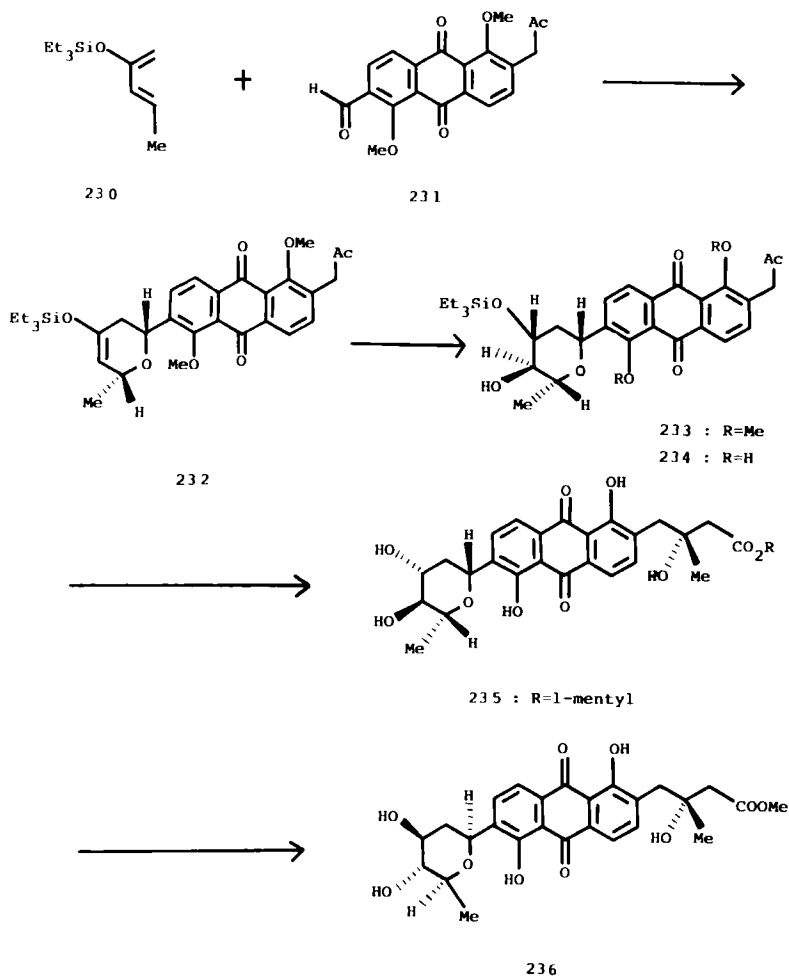
A Lewis acid-mediated hetero Diels–Alder reaction of a diene and an aldehyde was also applied as a route to subunits of monensin (**243**) (85JA6647). Reaction of aldehyde **237** with diene **176** in the presence of  $\text{Yb}(\text{fod})_3$  produced the silyl enol ether **238** as a single product in 56% yield. Treatment of **238** with HF in pyridine–methanol afforded a single ketone (**239**). Reduction of ketone **239** with sodium borohydride gave equatorial alcohol **240**. Methylation of **240** produced methyl ether **241**. Cleavage of the methyl glycoside linkage of **241** was accomplished through the action of dilute hydrochloric acid. Lactol **242** was treated with catalytic ruthenium dioxide in the presence of sodium metaperiodate. The lactonic acid was esterified with



SCHEME 31

diazomethane to afford the racemic lactonic methyl ester **243**. The monensin lactone was assembled by highly stereoselective steps (Scheme 33).

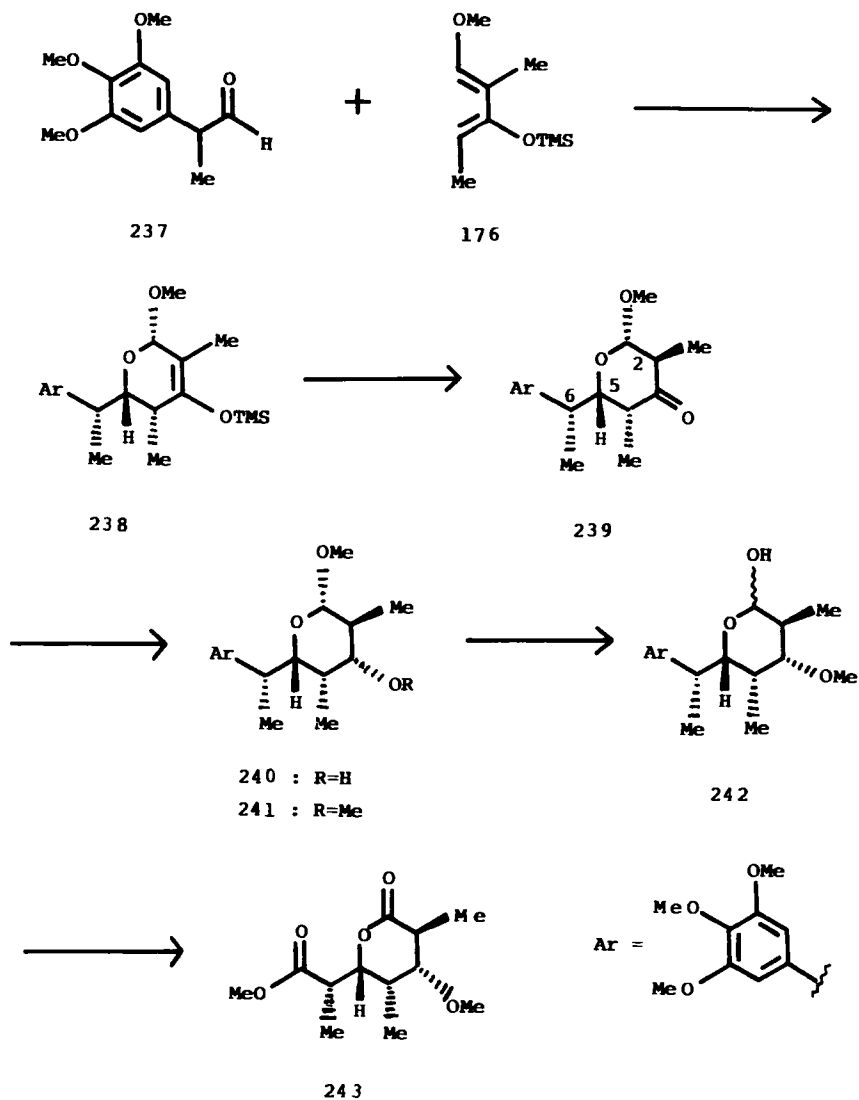
Danishefsky has also synthesized the key intermediate of tirandamycin, namely Ireland alcohol (**254**) (Scheme 34)(85JA6647). Reaction of 4,5-dimethylfurancarboxaldehyde (**244**) with diene **176** in the presence of  $Yb(fod)_3$  was followed by treatment of trifluoroacetic acid. The cis-substituted



SCHEME 32

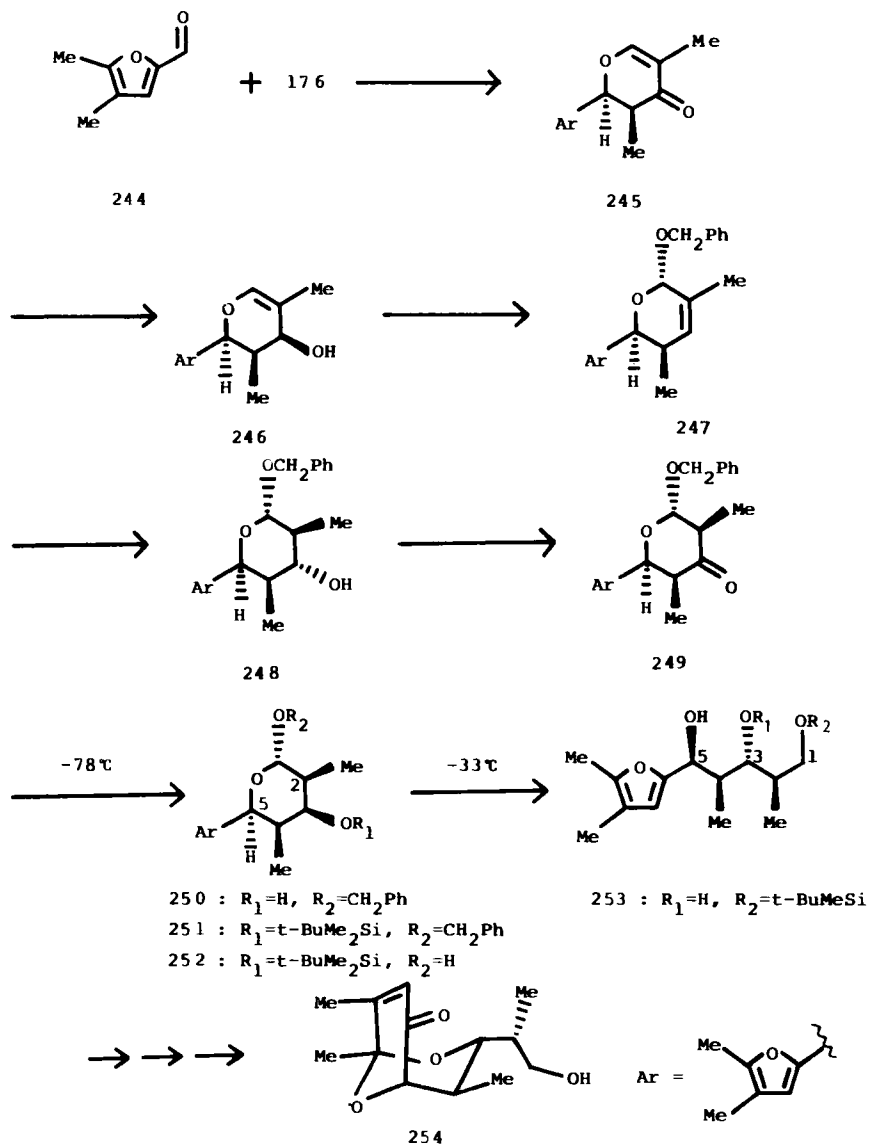
dihydropyrene **245** was obtained in 84% yield. Reduction of **245** with lithium aluminum hydride produced alcohol **246**. Exposure of **246** to benzyl alcohol in the presence of *p*-toluenesulfonic acid led to the branched pseudoglycal **247**. Hydroboration of **247** followed by oxidation gave a 10:1 ratio of two secondary alcohols. That the major compound (54%) is properly formulated as **248** was established upon completion of the sequence. Oxidation of **248** under Swern's conditions (81S165) afforded ketone **249**. Reduction of the ketone **249** occurred exclusively from the  $\alpha$ -face to afford the alcohol **250**, which was then converted to its *tert*-butyldimethylsilyl ether (**251**). Reductive debenzoylation of **251** under careful conditions gave the ring-opened product





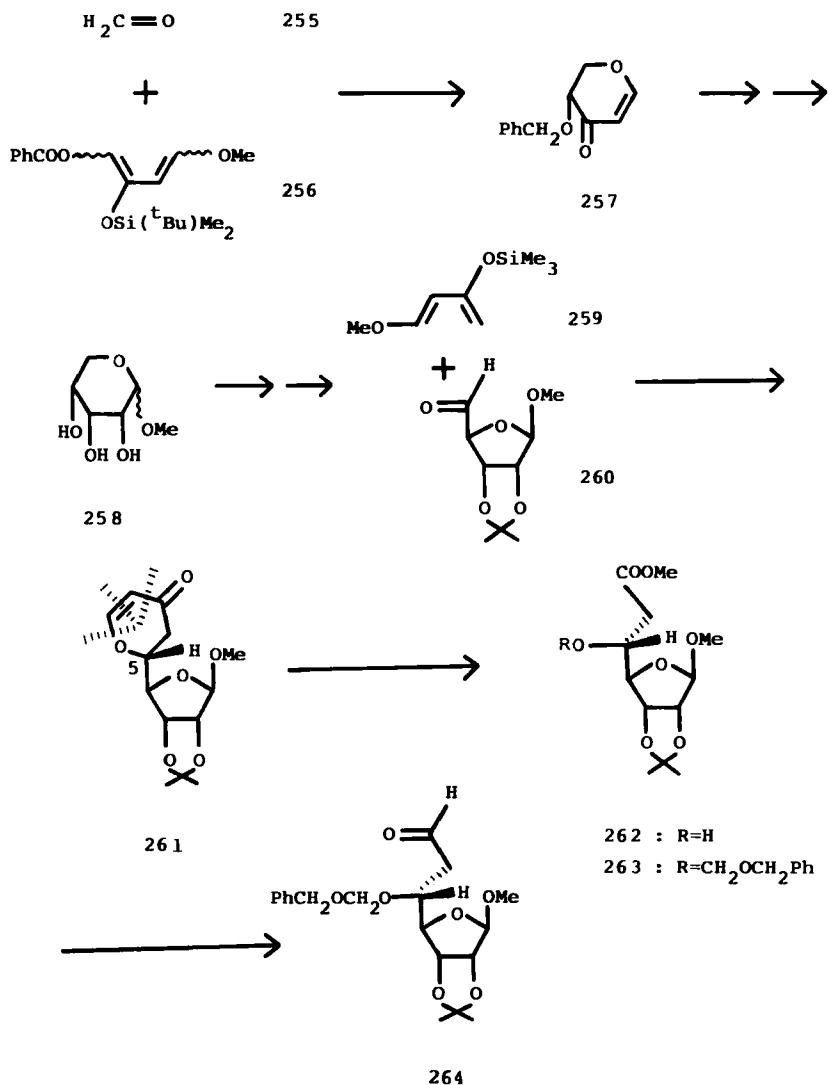
SCHEME 33

**253**, during which an unexpected transsilylation occurred. The oxidative treatment of the 2,3-dimethylfuranoid ring bearing a free hydroxyl on C-S, followed by desilylation and cyclization with HF in acetonitrile, afforded the Ireland alcohol **254** in low yield. This compound (**254**) can be converted to tirandamycin.



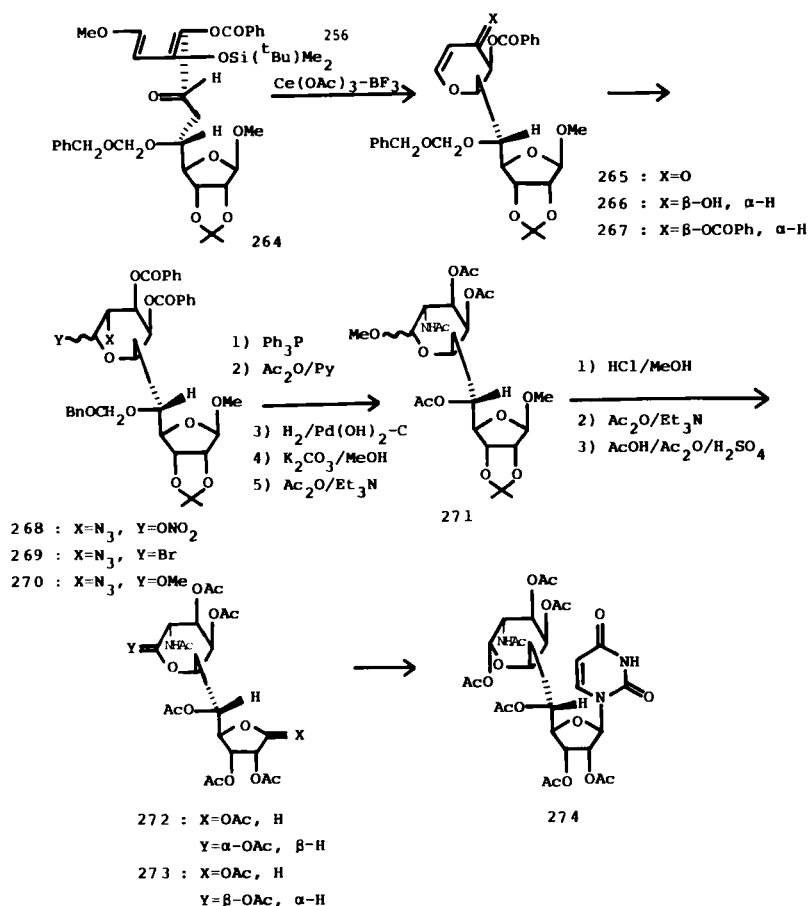
SCHEME 34

More recently, Danishefsky reported a fully synthetic route to tunicaminyluracil (**274**) derived from tunicamycin (85JA7761) and hikosamine (**284**) (85JA7762). Cyclocondensation of the ribosederived aldehyde (**260**) (84JOC1955) (Scheme 35) with diene **259** under catalysis by  $\text{Eu}(\text{fod})_3$  (83JA3716) afforded an 86% yield of the carbon-linked disaccharide **261**. Ozonolysis of **261**, followed by oxidative treatment and esterification, furnished the  $\beta$ -hydroxy ester **262** and its benzyloxymethyl ether **263**.



SCHEME 35

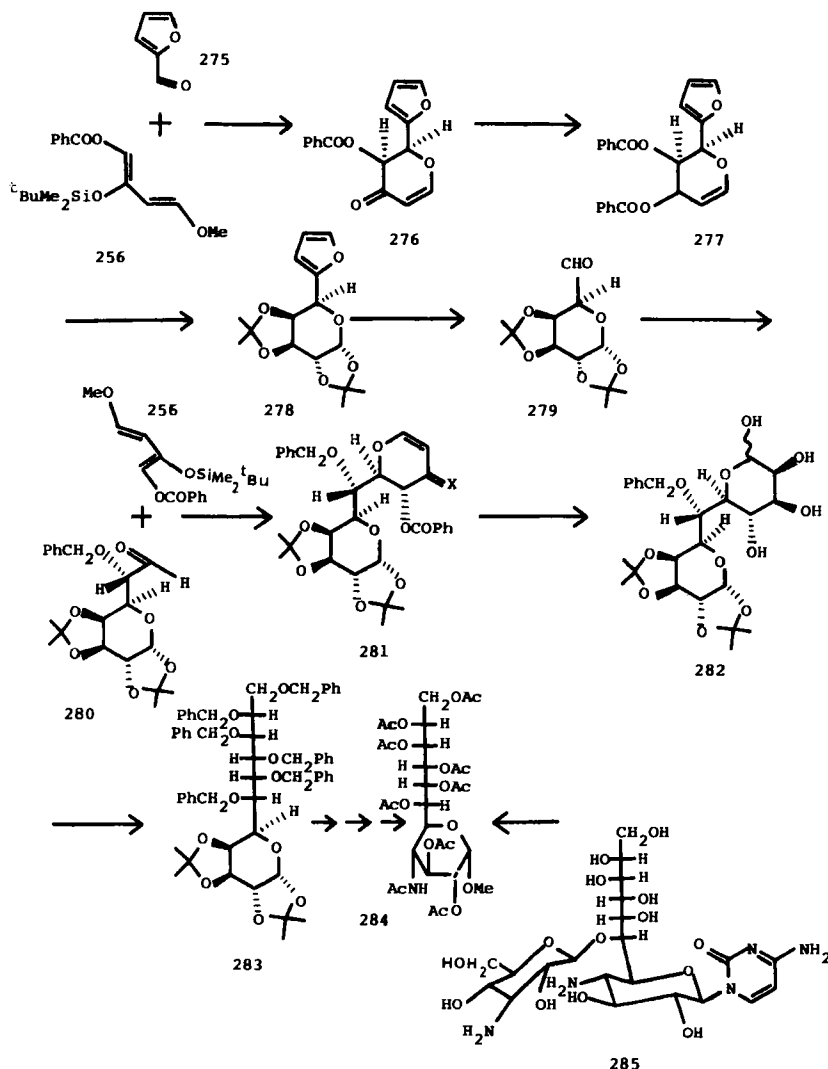
Aldehyde **264**, prepared from ester **263** in a two-step sequence, reacted with diene **256** in the presence of  $\text{Ce}(\text{OAc})_3 \cdot \text{BF}_3 \cdot \text{OEt}_2$  in toluene to give a single isomer (**265**). Reduction by Luche's procedure (79JA5848) gave alcohol **266**, which, on benzylation, provided dibenzoate **267**. Azidonitration according to Lemieux (79CJC1244) gave the anomeric nitrates **268**, which were converted to a single bromide by lithium bromide in acetonitrile and then by methanolysis [ $\text{AgOTf}(\text{Me}_2\text{N})_2\text{CO}$ , THF] to the methyl galactoside **270**. Transformation of **270** to **271** was achieved by a five-step sequence (Scheme 36). Cleavage of the acetonide **271** of the anomeric mixture was accomplished by methanolic hydrogen chloride. The resultant diol gave the tunicamine derivative **272** as an anomeric mixture of galactosides. Acetolysis of the anomeric methoxyl groups afforded a 1:1 mixture of anomeric acetate in the



SCHEME 36

hexose ring. The galactosyl anomers were separated by HPLC into **272** and **273**. Treatment of **272** with 2,4-bis(trimethylsilyl)oxypyrimidine gave a 50% isolated yield of (heptaacetyltonicaminy)uracil (**274**).

On the other hand, hikosamine (**284**), obtained by degradation of hikizimycin (**285**), was synthesized by the recently developed diene-aldehyde cycloaddition reaction (85JA7762). Hexoaldose **278** was synthesized starting with the  $\text{Eu}(\text{fod})_3$  (83JA3716) mediated cyclocondensation of furfural (**275**) with diene



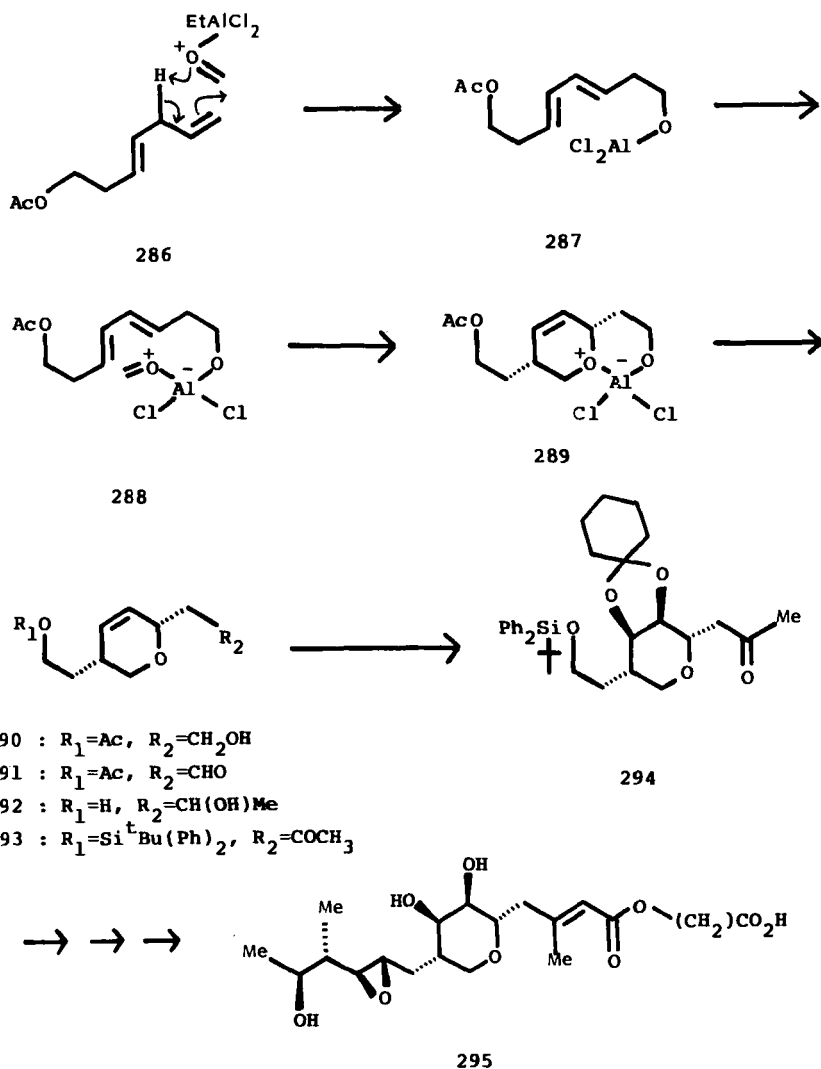
SCHEME 37

**256**. Subsequent treatment with trifluoroacetic acid afforded adduct **276** in 55–60% yield. Reduction with  $\text{NaBH}_4\text{--CeCl}_3$  gave an alcohol, which on benzoylation yielded the dibenzoate **277**. Hydroxylation of **277** followed by (i) acetalization, (ii) debenzoylation, and (iii) acetalization provided the furyl bisacetone **278**. Oxidative cleavage of the furan, followed by reduction of the resultant carboxylic acid with diborane, provided a racemic alcohol. After oxidation of this alcohol to aldehyde **279**, allylation (85TL823) of **279** afforded carbinol and thence the benzyl ether by benzyl bromide. Ozonolytic cleavage led to the aldehyde, which was converted to enol acetate and thence by ozonolytic cleavage to the heptaldose **280**. Once again, magnesium bromide-mediated cyclocondensation of aldehyde **280** with diene **256** afforded a 75% yield of the undecose **281**. Reduction of **281** gave the equatorial alcohol. Henbest-type (56CI(L)659) epoxidation of the allylic alcohol followed by debenzoylation with potassium carbonate in methanol provided hemiacetal **282**. Reduction of the hemiacetal system with lithium borohydride, followed by perbenzoylation of the resultant pentanol, produced hexabenzyl derivative **283**. The synthetic route to methyl peracetyl- $\alpha$ -hikosamine (**284**) was established with a nine-step sequence from **283** via the introduction of the 4- $\alpha$ -amino function. A synthesis of hikosamine based on internal asymmetric induction for the control of the 10 contiguous hetero-bearing chiral centers had been accomplished (Scheme 37).

## 2. Intramolecular Cycloaddition Reactions

A few rare instances of intramolecular carbonyl Diels–Alder cycloaddition reactions exist (82T3087).

Snider and Phillips (82JA1113) have brilliantly combined an ene reaction with a carbonyl Diels–Alder cycloaddition to produce pyran **290**, a key intermediate in a total synthesis of pseudomonic acid (**295**) (Scheme 38). The acetate **286**, prepared from a 1,5-diene (80TL1815), was treated with formaldehyde and ethyl aluminum dichloride to give 35–40% of pyran **290**. This transformation presumably involves an initial ene reaction of **286** to give the ene adduct **287**, which reacted with formaldehyde to produce complex **288**. A quasi-intramolecular Diels–Alder cycloaddition then ensued which led to **289**. Hydrolysis of the aluminum complex **289** gave the pyran **290** in a three-step sequence from **286**. Oxidation of **290** with pyridinium chlorochromate gave the aldehyde **291**. Addition of the crude aldehyde to excess methylmagnesium chloride afforded the diol **292**. Selective silylation of **292** followed by oxidation of the secondary alcohol gave the methyl ketone **293**. *cis*-Hydroxylation of **293** with osmium tetroxide followed by protection of the diol as the cyclohexylidene ketal gave the known intermediate **294**, identical with material prepared by Kozikowski *et al.* (80JA6577; 81TL2059).



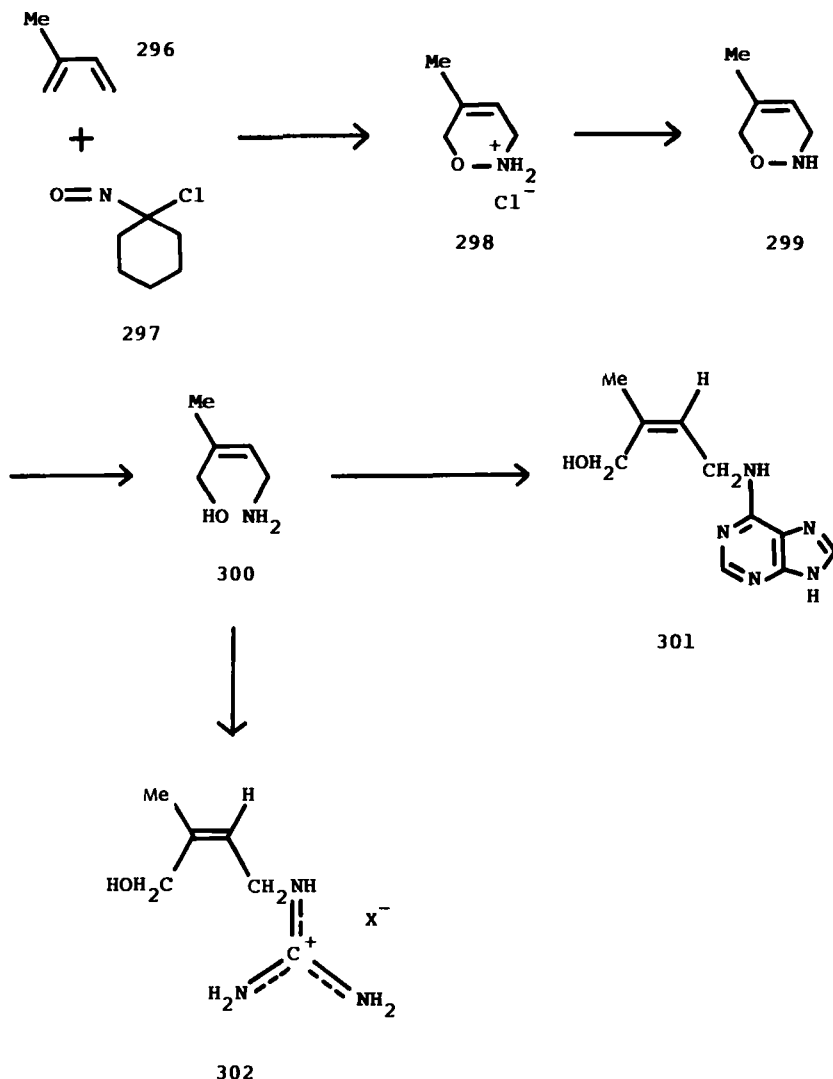
SCHEME 38

C.  $\text{N}=\text{O}$  DIENOPHILES

## 1. Intermolecular Cycloaddition Reactions

Nitroso compounds of various structural types have been widely utilized as Diels-Alder dienophiles, and the subject has been comprehensively reviewed several times (77CSR1; 82T3087). It has been known for many years that  $\alpha$ -chloronitroso compounds react with 1,3-dienes to yield unstable adducts of

the dihydro-1,2-oxazine type. Leonard (71JA3056) used the dihydro-1,2-oxazine **299** as a key intermediate in the total synthesis of the cell-division stimulant *cis*-zeatin (**301**) (Scheme 39). Diels-Alder reaction between isoprene (**296**) and 1-chloro-1-nitrosocyclohexane (**297**) in the presence of hydroquinone, followed by basification, gave oxazine **299**. It was reduced by zinc in acetic acid to 4-hydroxy-3-methyl-*cis*-2-butenylamine (**300**), which was used directly in the reaction with 6-chloropurine in refluxing *n*-butyl alcohol. The products were separable geometrical mixtures of zeatin (**301**). Final proof



SCHEME 39

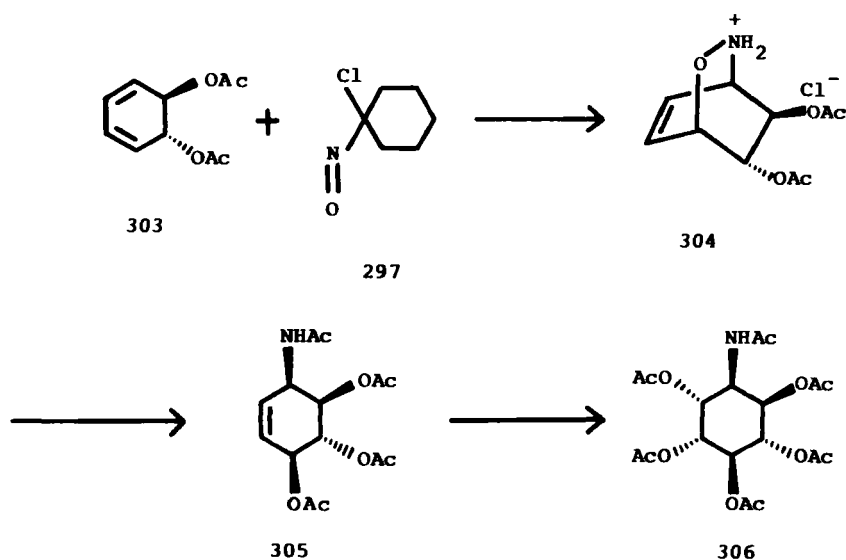


that the synthesis leading to 6-(hydroxy-3-methyl-*cis*-2-butenylamino)purine (**301**) had been stereoselective was achieved by hydrogenolysis of the product to give dihydrozeatin, identified by comparison with an authentic dihydrozeatin. Furthermore, the crude amino alcohol **300** was used directly in the reaction with *S*-methylisothiurea sulfate, and the product was converted into its salt for comparison with natural hydroxygalegine (**302**) by Leonard (72CC133).

Krestze's group (81LA202; 81LA210; 81LA224; 81LA610) has used a nitroso Diels–Alder reaction in the synthesis of konduramin-F1 tetraacetate (**305**) including inosamine derivative **306**. Diels–Alder reaction between the chloronitroso compound **297** and cyclohexadiene derivative **303** in alcohol gave the adduct **304** with methanolic ammonia. Reduction of **304** with zinc and hydrochloric acid afforded the ring-opened amino alcohol. Acetylation of the amino alcohol gave konduramin-F1 tetraacetate (**305**). The inosamine derivative **306** had been synthesized from the konduramin derivative **305** (Scheme 40) (81LA224).

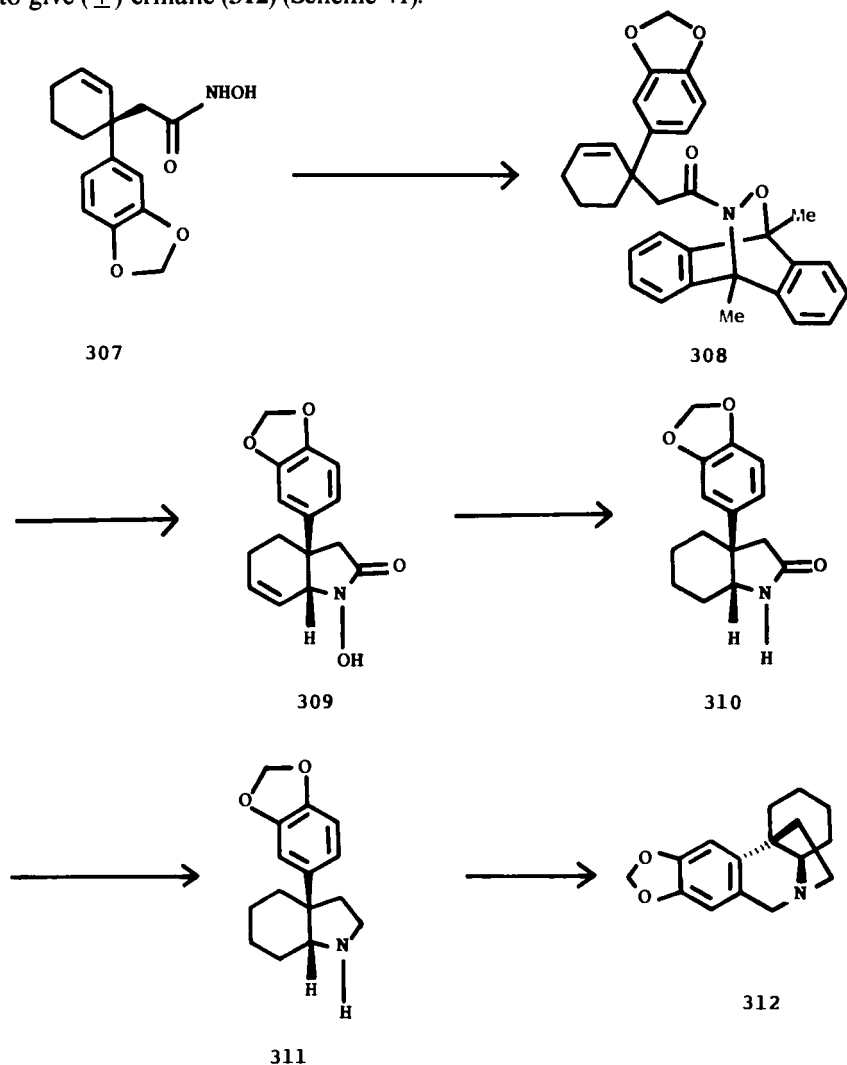
Kirby discovered that electron-deficient acylnitroso and cyanonitroso compounds can be readily generated, and that these species are excellent dienophiles (77CSR1).

In 1981, Keck and Webb applied this methodology to the synthesis of ( $\pm$ )-crinine (**312**) (81JA3173), ( $\pm$ )-mesembrine (**320**) (82JOC1302), and dihydromaritidine (**324**) (82JOC1302) having the perhydroindole skeletons of Amaryllidaceae alkaloids. The hydroxamic acid **307** was oxidized by tetra-



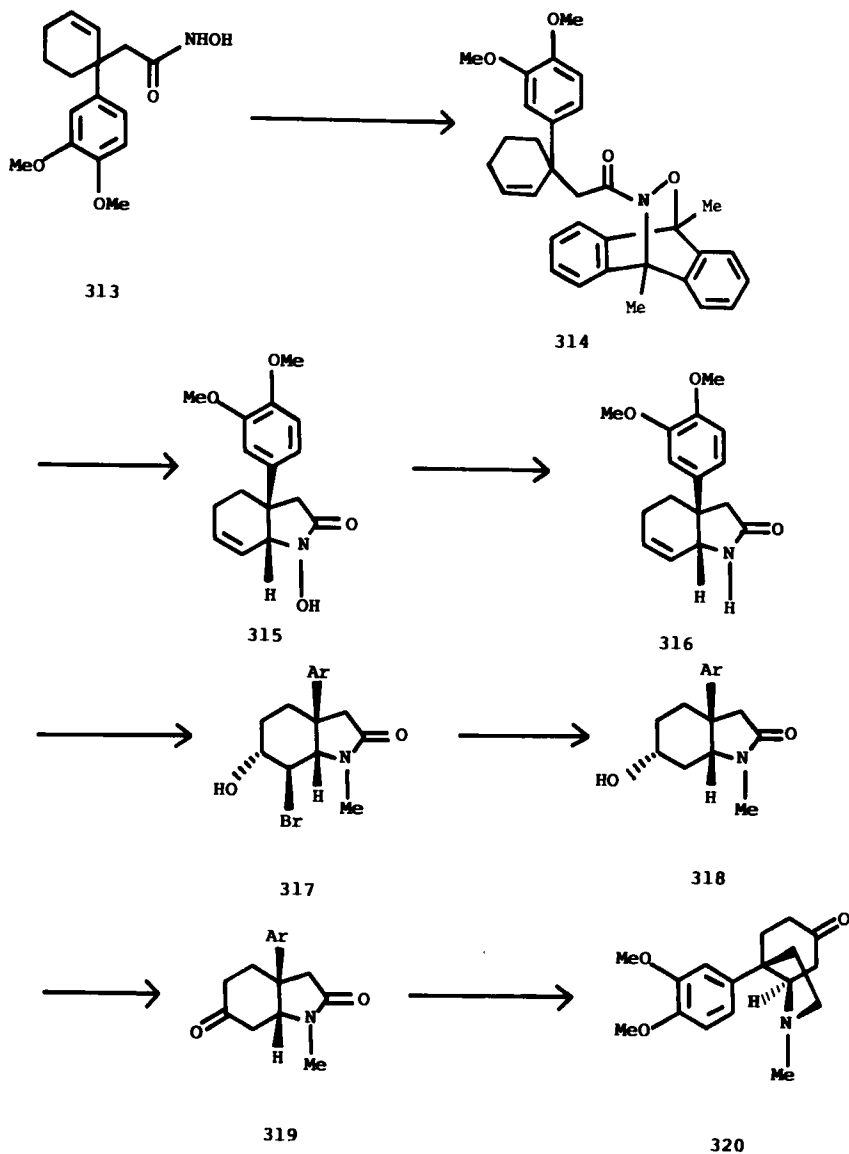
SCHEME 40

propylammonium periodate in the presence of 9,10-dimethylantracene to give the N=O Diels–Alder adduct **308** in 85% yield. Thermal release of the acylnitroso moiety with a concomitant ene reaction was effected by heating the adduct **308** at reflux in toluene to afford the desired cyclic hydroxamic acid **309**. Reduction of **309** with  $\text{TiCl}_3$  followed by hydrogenation gave lactam **310**, which was reduced by lithium aluminum hydride to yield secondary amine **311**. Finally, the amine **311** was subjected to a Pictet–Spengler reaction to give ( $\pm$ )-crinane (**312**) (Scheme 41).

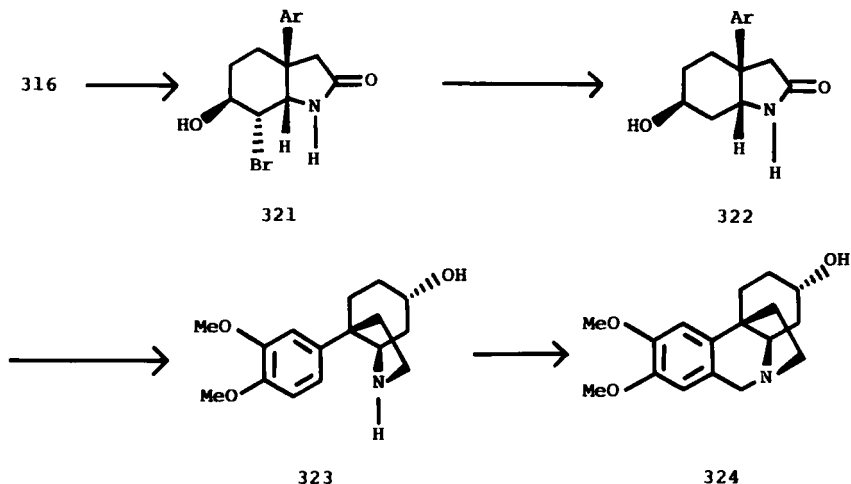


SCHEME 41

Similarly (Scheme 42) (82JOC1302), oxidation of hydroxamic acid **313** in the presence of 9,10-dimethylantracene gave an 82% yield of the hetero Diels–Alder adduct **314**. This product was decomposed in refluxing toluene to afford a quantitative yield of the ene adduct **315**. The cyclic hydroxamic acid **315** was converted to the corresponding lactam (**316**) by  $\text{TiCl}_3$  reduction. The



SCHEME 42

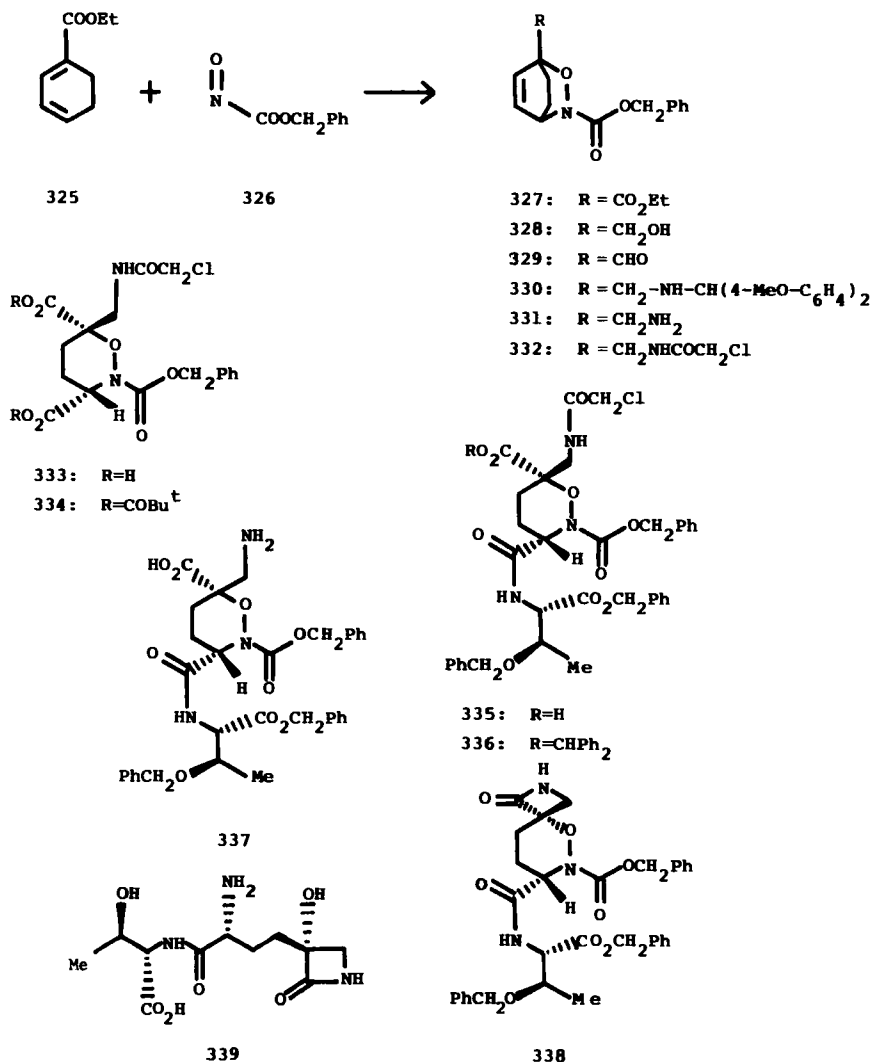


SCHEME 42 (continued).

*N*-methylated lactam was treated with *N*-bromosuccinimide (NBS) to give bromohydrin **317**. Removal of bromine via tin hydride reduction gave alcohol **318**, and then oxidation with pyridinium chlorochromate proceeded smoothly to give the keto lactam **319**. Treatment with ethylene glycol in refluxing benzene containing a trace of *p*-toluenesulfonic acid gave a crude ethylene ketal, which was then reduced with lithium aluminum hydride to the amino ketal. The crude amino ketal was hydrolyzed with dilute hydrochloric acid. Racemic mesembrine **320** was obtained. On the other hand, treatment of lactam **316** with NBS gave the bromohydrin **321**. Removal of the bromine by tin hydride reduction gave alcohol **322**, which yielded the known amine **323** upon reduction with lithium aluminum hydride. Pictet–Spengler cyclization of **323** (or treatment with Eschenmoser's salt) gave ( $\pm$ )-dihydromaritidine (**324**).

Baldwin's group elegantly utilized the  $N=O$  cycloaddition strategy in the first stereospecific total synthesis of tabtoxin (Scheme 43) (83CC1049; 84T3695). The diene ethyl cyclohexa-1,3-diene carboxylate (**325**) was treated with benzyl nitrosoformate (**326**), generated *in situ* from *N*-benzyloxycarbonyl hydroxylamine and tetrabutylammonium periodate. A single product (**327**) was formed exclusively in 93% yield. The regiochemistry of adduct **327** was established by chemical analysis and X-ray crystallography. Reduction with sodium borohydride gave the alcohol **328**, oxidized by Moffat oxidation to the aldehyde **329**. The aldehyde **329** was converted to the protected amine **330** with 4,4'-dimethoxybenzhydramine and sodium cyanoborohydride. Deprotection of **330** with trifluoroacetic acid gave the amine **331**, which was then

converted into the chloroacetamide **332**. Oxidative cleavage of the double bond was achieved by potassium permanganate in the presence of tetrabutylammonium sulfate to provide the racemic diacid **333**. The diacid **333** was converted to dipivaloyl mixed anhydride **334**, which reacted *in situ* with *O*-benzyl-L-threonine benzyl ester to give the amide **335** resulting from selective attack at the less hindered of the two carbonyl groups. A mixture of diastereomers was formed, which was then converted into the benzhydryl esters **336**. One of the isomers of **336** was deprotected to the acid and then



SCHEME 43

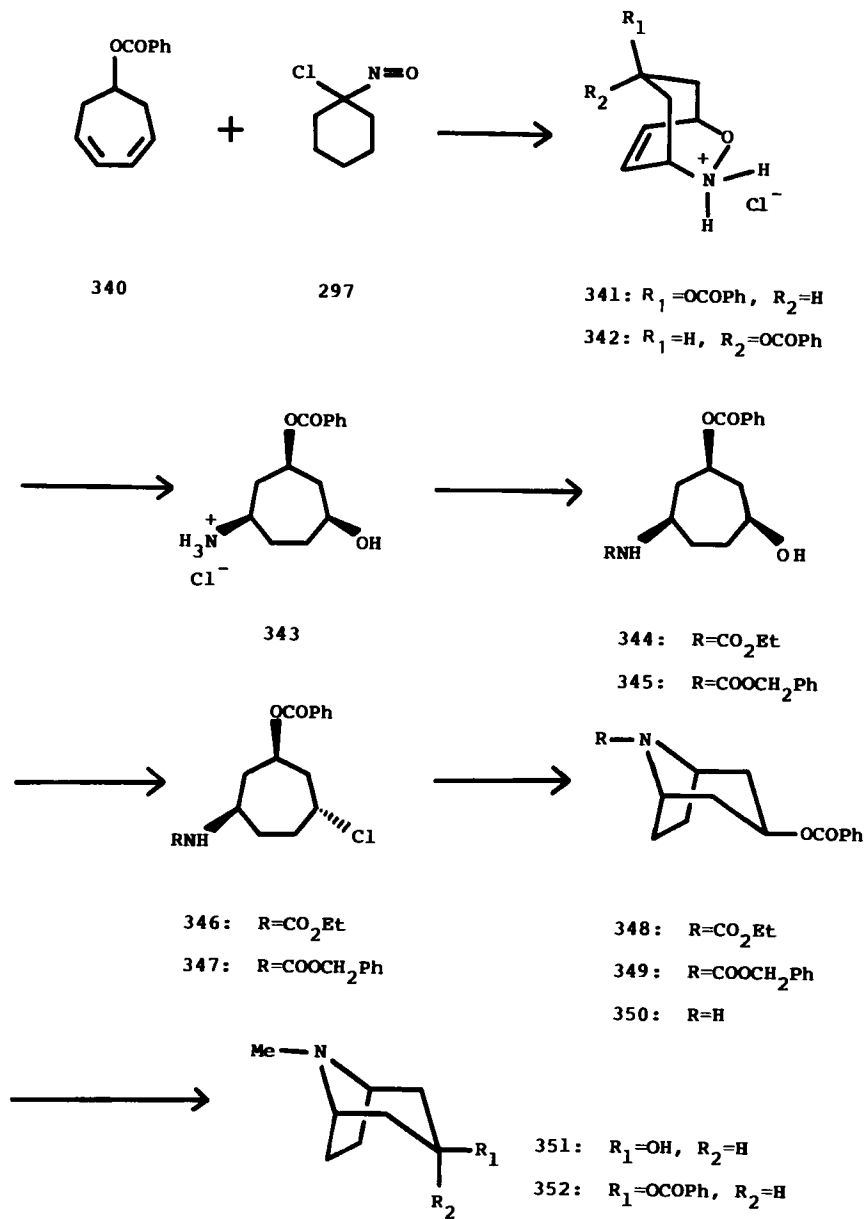
further deprotected to the amino acid **337** by thiourea. The resultant product was directly cyclized to the spirocyclic  $\beta$ -lactam **338** by thiopyridine disulfide and triphenylphosphine. Hydrogenolysis of **338** gave tabtoxin (**339**).

Recently, Kibayashi's group (84TL5094) reported the new synthetic route to pseudotropine (**351**) and tropacocaine (**352**) (tropan alkaloids) via intermolecular nitroso cycloaddition. An intermolecular nitroso cycloaddition of 1-chloro-1-nitrosocyclohexane (**297**) with cyclohepta-1,3-diene **340** in carbon tetrachloride/ethanol at  $-20^{\circ}\text{C}$  generated a mixture of the oxabicyclononane hydrochlorides **341** and **342** (72%). The separable major adduct (**341**) was converted to pseudotropine (**347**) (Scheme 44). Catalytic hydrogenation of **341** gave the amino alcohol hydrochloride **343**, which was then subjected to selective N-acylation to give the carbamate **344**. Chlorination with thionyl chloride followed by intramolecular cyclization of **344** afforded ethoxycarbonylnortropine (**348**). Reduction of **348** with lithium aluminum hydride provided pseudotropine (**351**). However, benzyloxycarbonylation of **343** gave carbamate **345**, which was chlorinated with thionyl chloride to yield **347**. The base-induced cyclization of **347** afforded the tropan nucleus (**349**). Deprotection of **349** by catalytic hydrogenation gave *N*-nortropacocaine (**350**). *N*-Methylation provided tropacocaine (**352**).

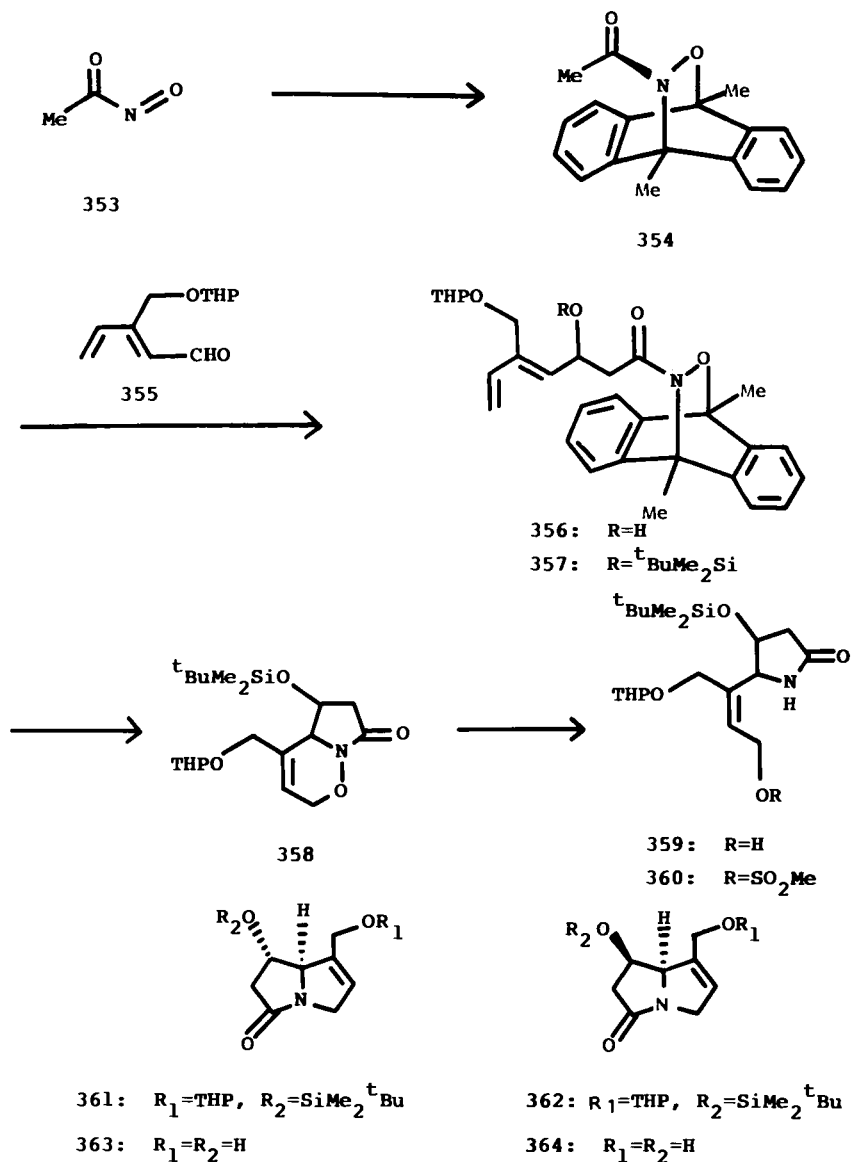
## 2. Intramolecular Cycloaddition Reactions

The acylnitroso cycloaddition adduct has been used in a total synthesis of the necine bases heliotridine (**363**) and retronecine (**364**) based on the intramolecular dienophile transfer by Keck (80JA3632). Diels–Alder reaction between acylnitroso compound **353** and 9,10-dimethylantracene afforded adduct **354** quantitatively (78TL4767). Aldehyde **355** was condensed with the carbanion derived from deprotonation of adduct **354** to afford the alcohol **356**. After hydroxyl protection of **356** to yield **357**, heating the diene **357** in benzene caused a retro Diels–Alder reaction, giving an acylnitroso compound, which underwent intramolecular cycloaddition to give the 1,2-oxazine **358**. Reductive cleavage of the N—O bond in **358** with 6% sodium amalgam yielded the hydroxylactam **359**. Hydroxylactam **359** was converted into the corresponding mesylate **360**, then treated with lithium diisopropylamide (LDA) in THF to give the separable bicyclic lactams **361** and **362**. Each bicyclic lactam structure was confirmed by conversion into ( $\pm$ )-heliotridine (**363**) and ( $\pm$ )-retronecine (**364**) (Scheme 45).

Recently, Kibayashi's group (85JA5534) elegantly carried out the stereocontrolled total synthesis of gephyrotoxin (skin extracts of neopropical poison dart frog) based upon an intramolecular nitroso Diels–Alder reaction. The hydroxamic acid **365** was treated with tetrapropylammonium periodate



SCHEME 44

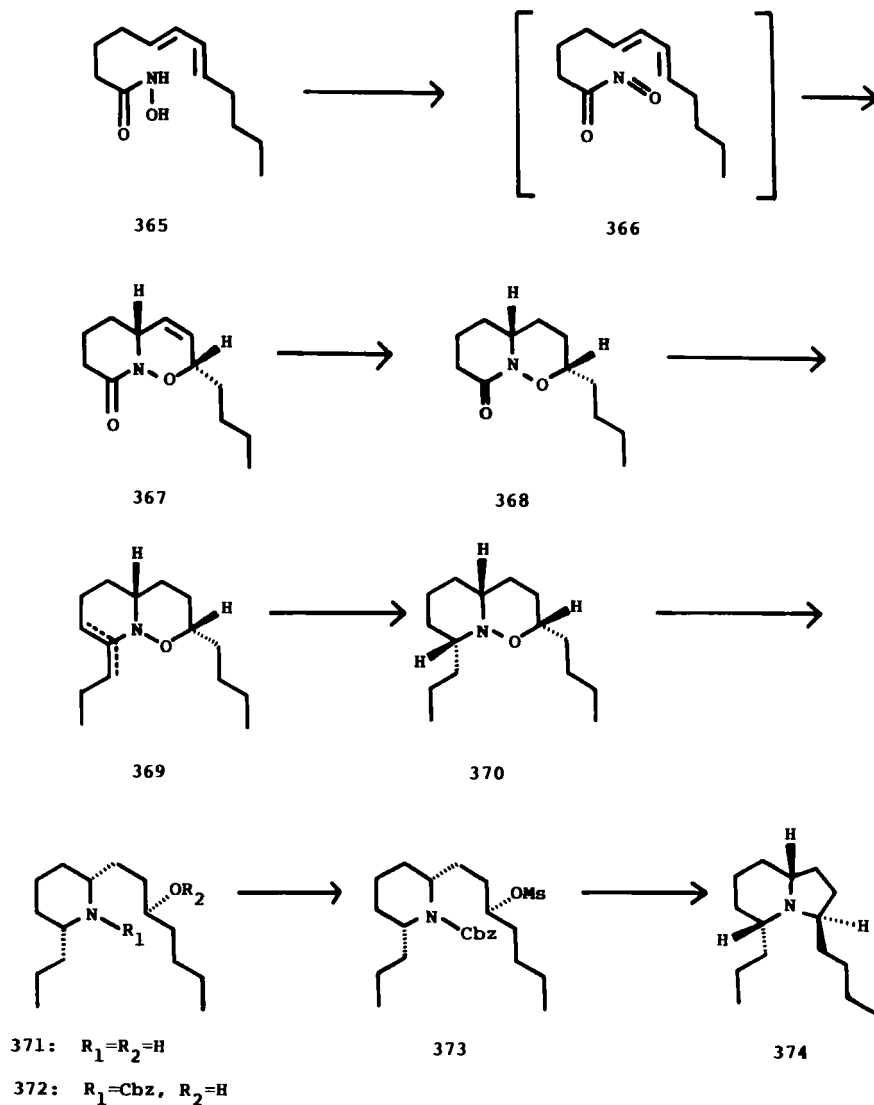


SCHEME 45; THP = tetrahydropyranyl.

to generate *in situ* the acylnitroso intermediate **366**, which underwent intramolecular [4 + 2]-cycloaddition to give the 1,2-oxazine derivative **367** (82%). Hydroboration of **367** provided **368**. Treatment of compound **368** with propylmagnesium bromide gave unstable enamine **369**, which was reduced



with sodium cyanoborohydride in methanol to **370** exclusively. Reductive cleavage of the N—O bond in **370** gave the amino alcohol **371**. Exposure of this product to benzyl chloroformate in alkali furnished the hydroxy carbamate **372**, along with two other products. Finally, the hydroxy carbamate **372** was converted to the mesylate **373**, which upon hydrogenation provided ( $\pm$ )-gephyrotoxin 223AB (**374**) (Scheme 46).



SCHEME 46; CBz = Carbobenzyloxy.

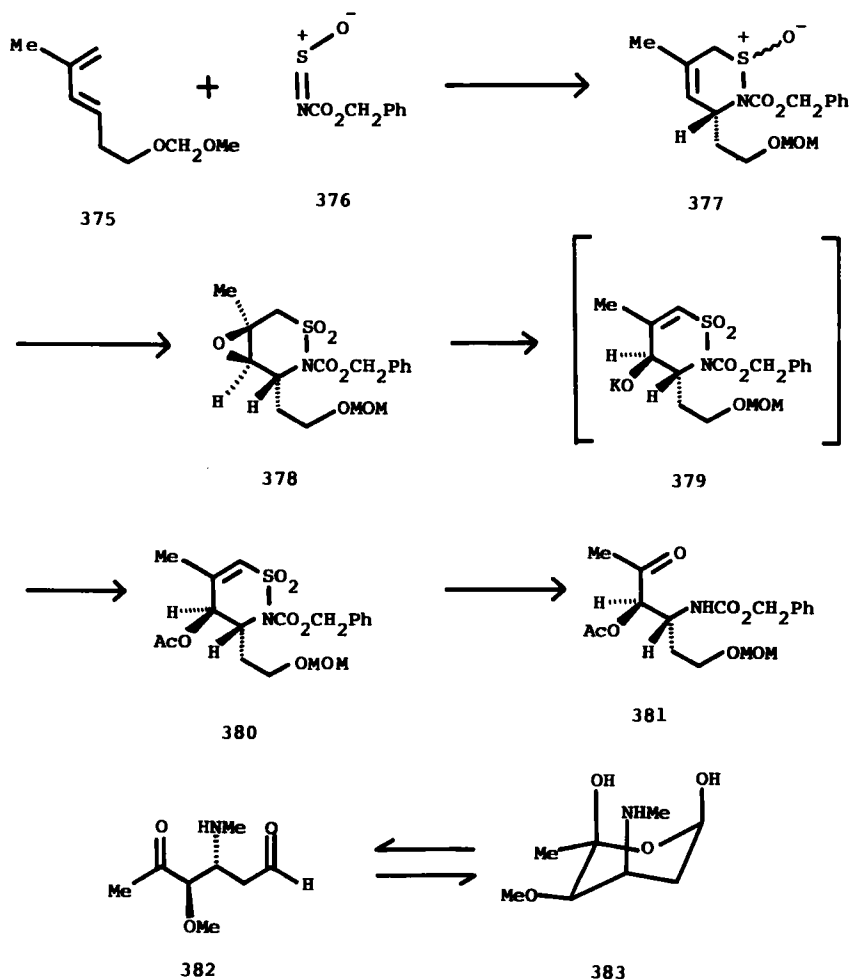
D.  $N=S$  DIENOPHILES1. *Intermolecular Cycloaddition Reactions*

Intermolecular Diels–Alder reactions of various *N*-sulfinyl compounds with 1,3-dienes to form 3,6-dihydrothiazine 1-oxide have been known for many years (67AG(E)49). Cycloaddition reactions using imines of sulfur oxide as dienophiles are well documented in a previous review (82T3087). Weinreb's group (83TL987) established the Mock–Nugent (78JOC3433) retro-ene mechanism by the stereo-controlled synthesis of unsaturated amines (*E*)-*threo*- and (*E*)-*erythro*-homoallylamine. They further developed a simple procedure for the stereospecific synthesis of unsaturated, acyclic, vicinal, amino alcohols (83JA4499) and unsaturated diamines (84JA7867) via an intermolecular *N*-sulfinyldienophile Diels–Alder reaction. This is followed by cleavage of the  $N-S$  bond with a nucleophile and then by [2,3]-sigmatropic rearrangement of the allylic sulfoxide or allylic sulfilimine-type of intermediate (84H309; 84JA7861).

They applied the intermolecular *N*-sulfinyldienophile Diels–Alder reaction to the synthesis of the structurally unique microbial metabolite staurosporine with an amino sugarlike moiety. In this approach to the amino sugarlike component **383**, the synthesis of the keto aldehyde **382**, which is equivalent to **383**, has been carried out as shown in Scheme 47 (84H309). Treatment of diene **375** with *N*-sulfinyl carbamate **376**, prepared *in situ* at room temperature, gave a separable mixture of adducts **377** (91%) differing only in their configuration at sulfur. Oxidation of adduct **377** with pertrifluoroacetic acid gave exclusively  $\beta$ -epoxysultam **378**. Treatment of **378** with potassium hydride afforded the unsaturated sultam alkoxide **379**, which was acetylated to give the acetate **380**. Ozonolysis of the acetate **380** produced the methyl ketone **381** having the desired erythro stereochemistry.

2. *Intramolecular Cycloaddition Reactions*

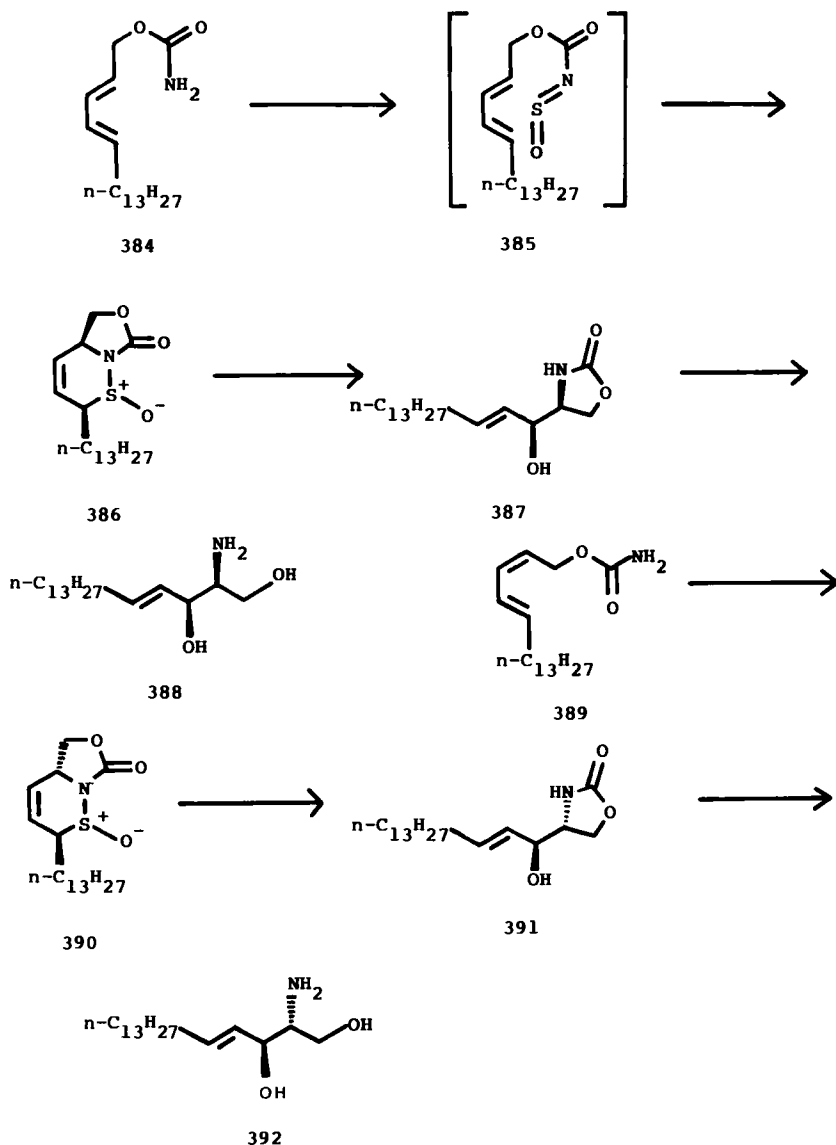
Weinreb's group has reported the first example of an intramolecular *N*-sulfinylimide Diels–Alder cycloaddition for the synthesis of *threo*-sphingosine (**388**) and *erythro*-sphingosine (**392**) (Scheme 48) (83JA4499; 84JA7861). Myristic aldehyde was transformed in three steps to (*E,E*)-carbamate **384**, which upon treatment with thionyl chloride/pyridine cyclized at room temperature to afford adduct **386** via **385** in 85% yield. Conversion of adduct **386** to the (*E*)-*threo* cyclic carbamate **387** was effected by phenylmagnesium bromide, followed by treatment with triethyl phosphite. Hydrolysis of the carbamate group of **387** gave racemic *threo*-sphingosine (**388**). On the other



SCHEME 47; MOM = methoxymethyl.

hand, for the synthesis of *erythro*-sphingosine (392), intramolecular Diels-Alder cycloaddition of the *N*-sulfinylcarbamate derived from the (*E,Z*)-carbamate 389 afforded the adduct 390 (85%). Conversion of adduct 390 to the *erythro* cyclic carbamate 391 was done in a similar way. Basic hydrolysis of the carbamate 391 gave *erythro*-sphingosine (392).

An intramolecular version of this methodology was further applied to construction of amino sugars, such as the unnatural C-5 epimer of desosamine (399) (84JOC3243) and deoxyaminopentose (406) (85T1143). When (*E,E*)-diene carbamate 393 was treated with thionyl chloride/pyridine between 0°C and room temperature, a single Diels-Alder adduct (395) was formed in 80% yield. The structure and stereochemistry of this dihydrothiazine oxide were

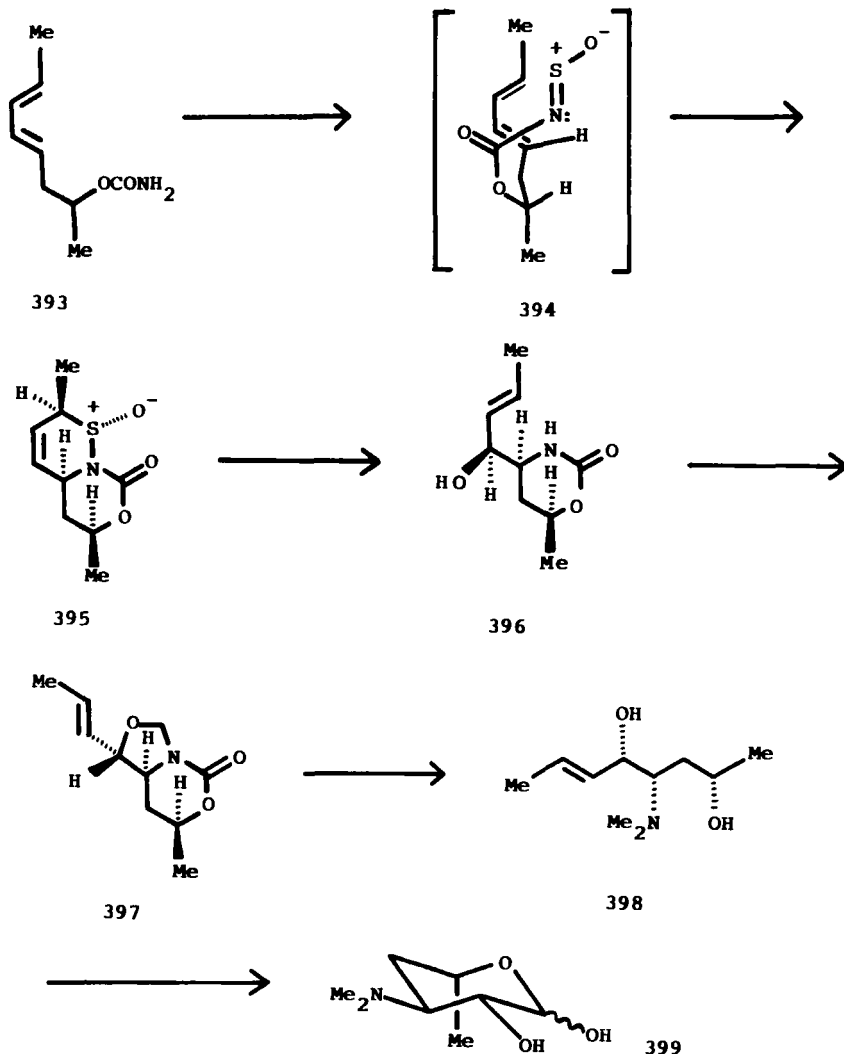


SCHEME 48

determined by X-ray analysis. In the transition state the bridging atoms were in a quasi-boat conformation as depicted in **394** with the quasi-equatorial methyl group. Diels–Alder adduct **395** was cleaved with phenylmagnesium bromide to give an allylic sulfoxide. A [2,3]-sigmatropic rearrangement and desulfurization of the resulting sulfenate ester yielded allylic alcohol **396** as a single isomer having the (*E*)-threo configuration (83JA4499; 84JA7861).

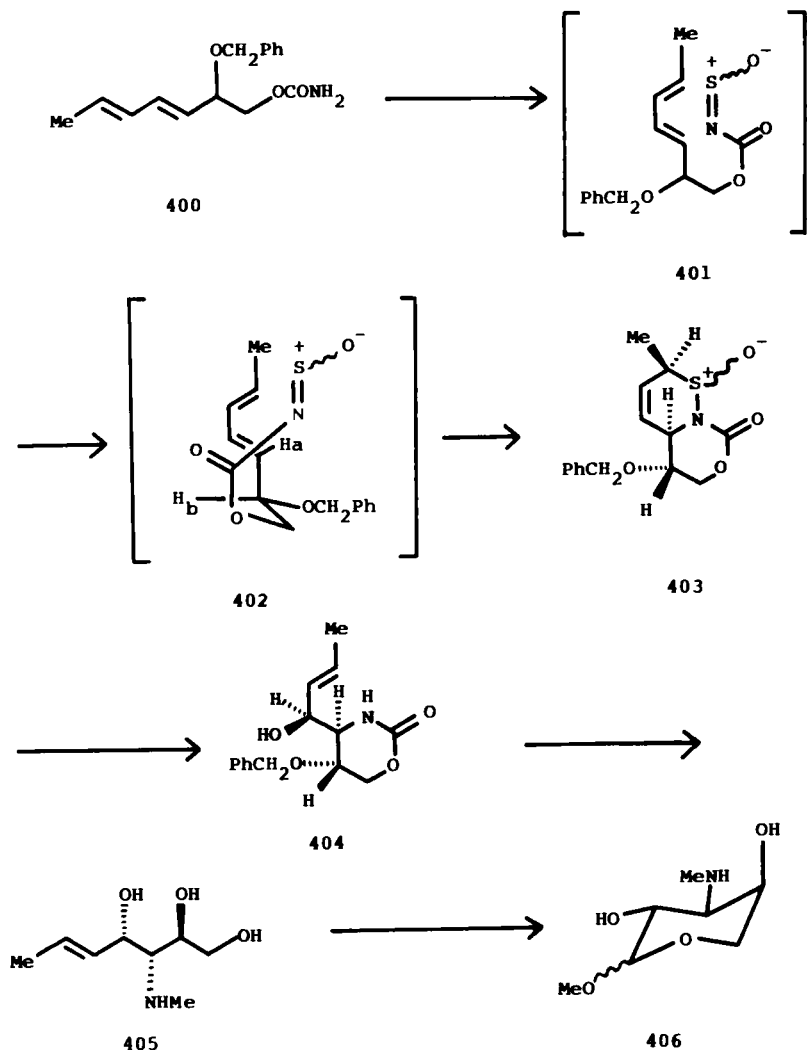
Reaction of allylic alcohol **396** with paraformaldehyde using a catalytic amount of *p*-toluenesulfonic acid gave cyclic carbamate **397**, which upon reduction with lithium aluminum hydride afforded aminodiol **398**. Oxidative cleavage of the double bond of **398**, achieved by dry silica gel ozonization (80JA5968) of the trifluoro acetate salt of aminodiol **398**, gave ( $\pm$ )-5-*epi*-desosamine (**399**) (Scheme 49).

Similarly, the carbamate **400** was treated with thionyl chloride. Dihydrothiazine *S*-oxide **403** was produced as an inseparable mixture (15:1) of sulfur



SCHEME 49

epimers through a Diels–Alder transition state resembling **402** (57%). The cycloadduct **403** was rearranged in a similar manner to give allylic alcohol **404** as a single stereoisomer. Reduction of **404** with lithium aluminum hydride gave an *N*-methylamine. Deprotection with sodium in liquid ammonia afforded *N*-methylaminotriol **405**. Aminotriol **405** was converted to its salt with *p*-toluenesulfonic acid, and this material was subjected to dry silica gel ozonolysis (80JA5968), followed by methanolic dimethyl sulfide reduction to afford deoxyaminopentose **406** as a 1:1 mixture of anomers (Scheme 50).



SCHEME 50

### III. Diel–Alder Reactions Using Heterobutadienes

#### A. 1-AZADIENE SYSTEMS ( $N=C-C=C$ )

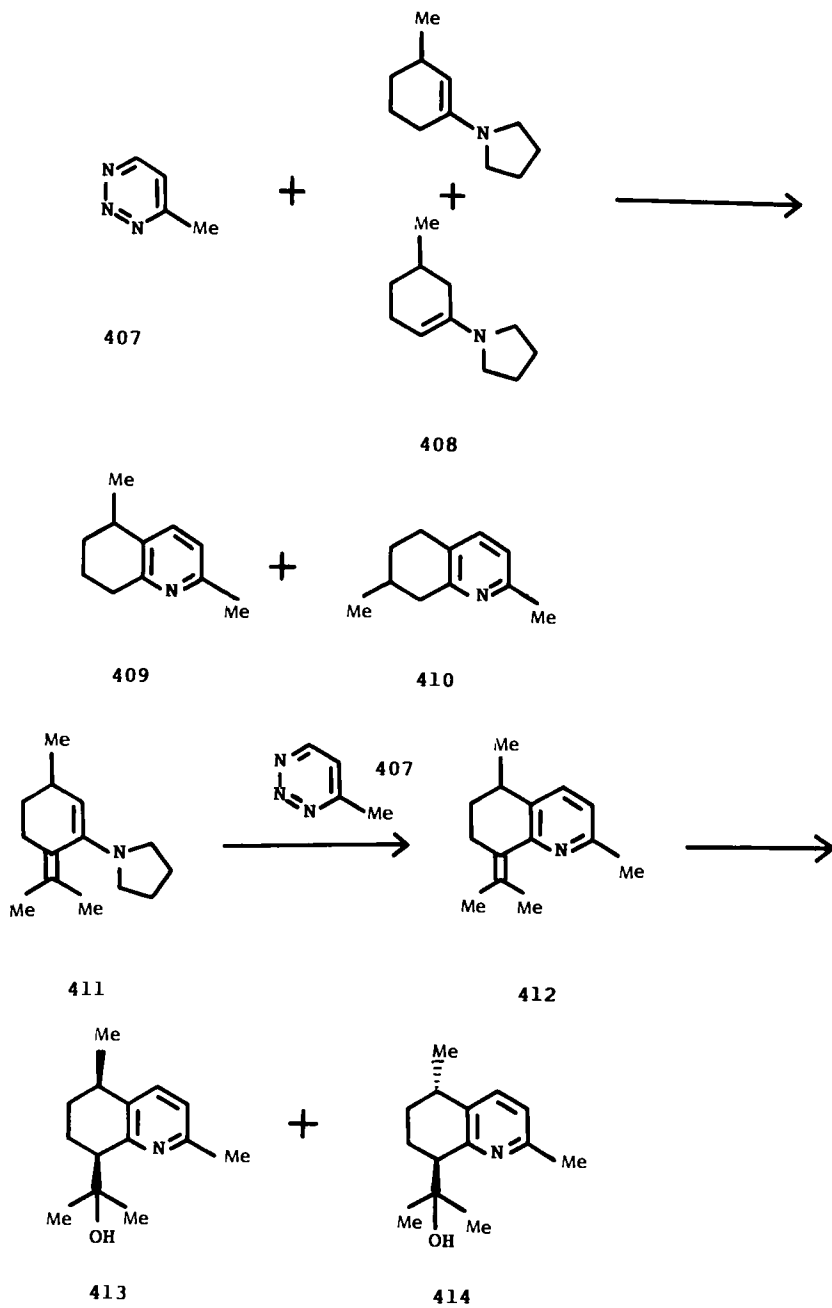
##### 1. Intermolecular Cycloaddition Reactions

It has been known for many years that 1-azadienes undergo a Diels–Alder reaction with a variety of dienophiles to give nitrogen-containing heterocycles (83T2869). However, the use of this intermolecular Diels–Alder reaction in the synthesis of natural products did not appear until recently. Sugita's group developed an intermolecular Diels–Alder reaction between heterocyclic 1-azadiene and cycloalkanone pyrrolidine enamines for the synthesis of the terpenoid alkaloid 2,5-dimethyl-5,6,7,8-tetrahydroquinoline (**409**) and fabianine (**413** and **414**) (Scheme 51) (85H2789; 86H29). Heating a mixture of 4-methyl-1,2,3-triazine (**407**) and enamine **408** in a sealed tube at 100°C gave the adduct **409** along with regioisomer **410** (1:4). Furthermore, treatment of enamine **411** with 1,2,3-triazine **407** in dry chloroform in a sealed tube at 100°C afforded the desired adduct **412** in 46% yield. Hydration of adduct **412** with 80% sulfuric acid gave fabianine (**413** and **414**) as a diastereomeric mixture (1:1).

##### 2. Intramolecular Cycloaddition Reactions

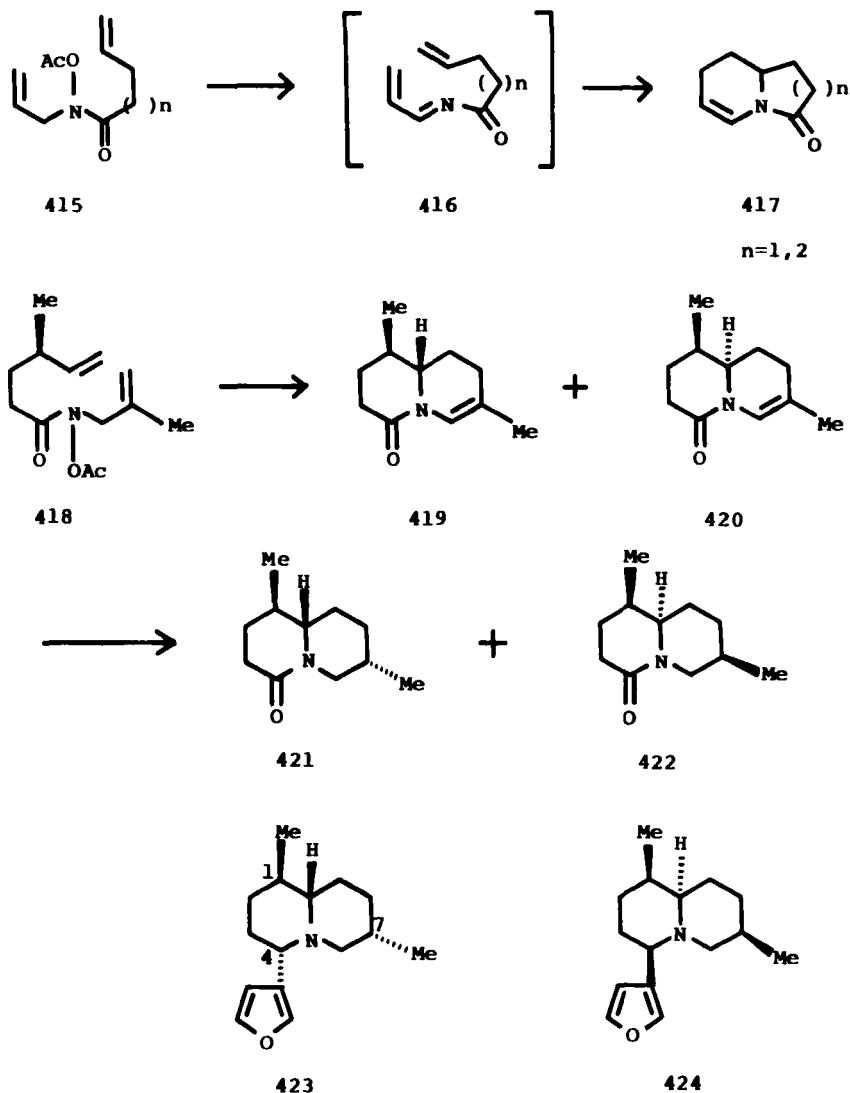
In 1981 Fowler's group (81JA2090) observed that *N*-acyl-1-azadiene **416** could be generated by thermal elimination of acetic acid from *N*-acyl-*O*-acetyl-*N*-allylhydroxylamines (**415**) and made to undergo intramolecular Diels–Alder reactions to give the indolizidine and quinolizidine systems **417** (83JA7696). This methodology was applied to the total synthesis of deoxynupharidine (**423**) and 1-epideoxynupharidine (**424**) (85JOC2719). Evaporation of **418** through a hot tube produced a 3:1 mixture of adduct **419** and its diastereomer **420** in 70% yield. Reduction of this mixture afforded a separable mixture of lactam **421** and its diastereomer **422** stereoselectively. Treatment of **421** with borane–dimethyl sulfide gave deoxynupharidine (**423**) along with its C-4 isomer (18:1). The synthesis of 1-epideoxynupharidine (**424**) was accomplished from **422** by using a similar procedure (Scheme 52).

Saegusa's group (81JA5250) found that [*o*-[(trimethylsilyl)alkylamino]-benzyl]trimethylammonium halide underwent the fluoride-anion induced 1,4-elimination under mild conditions to generate an *o*-quinone methide *N*-alkylamine intermediate. They performed the formal synthesis of gephyrotoxin **434** on the basis of an intramolecular cycloaddition of the *o*-quinone methide *N*-alkylamine **426** (83TL2881). Treatment of azadiene precursor **425**



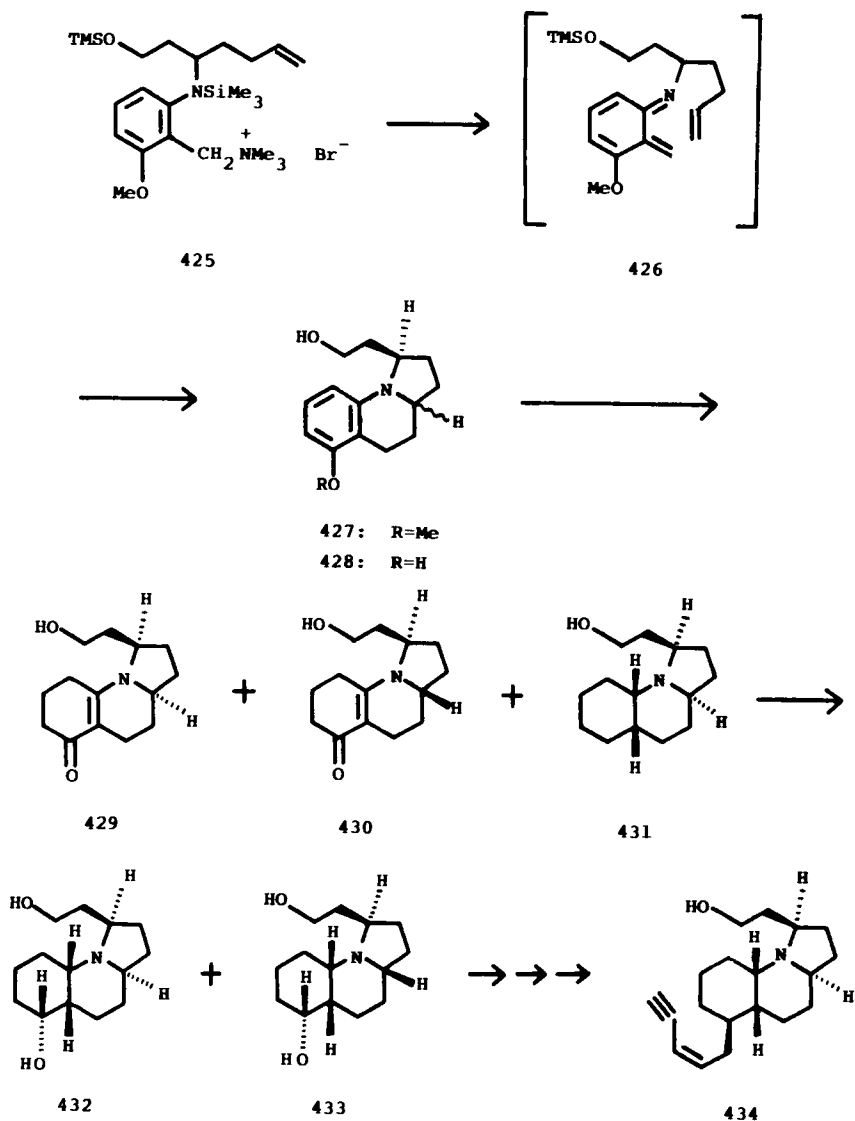
SCHEME 51





SCHEME 52

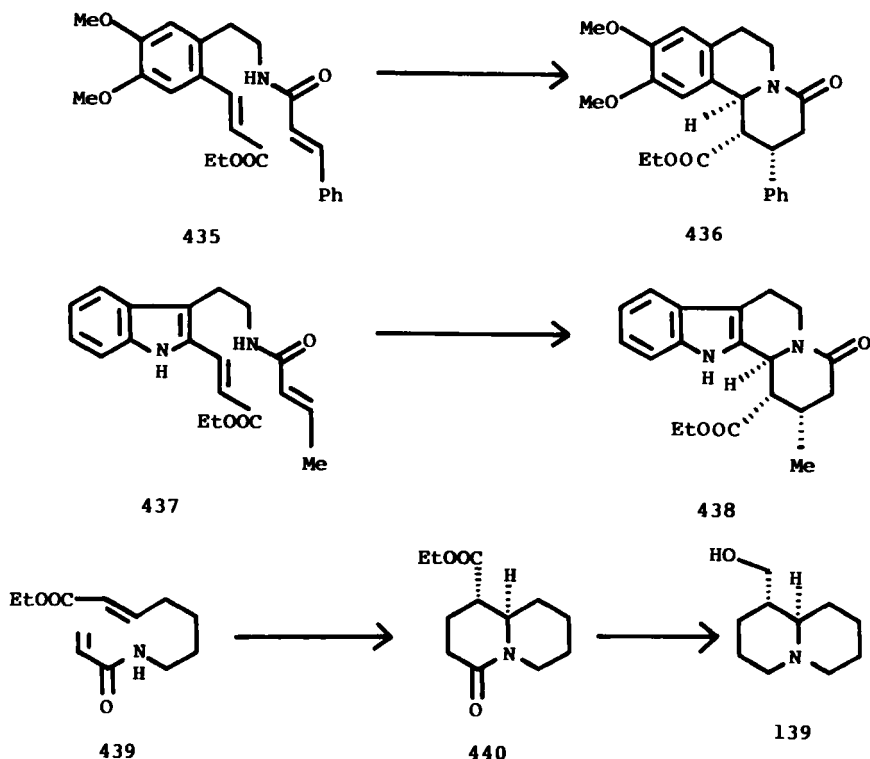
with CsF at 65°C afforded benzo[*e*]indolizidine derivative **427** as a mixture of *cis* and *trans* isomers. Reduction of phenol **428** with 5% Rh on alumina produced an inseparable unsaturated ketone (**429** and **430**) (75%). Stereo-selective hydrogenation of **429** and **430** with 5% Pt on alumina gave separable alcohols **432** and **433**. Transformation of enamino ketone **429** to gephyrotoxin **434** via **432** has already been established by Kishi (Scheme 53) (81TL4197).



SCHEME 53

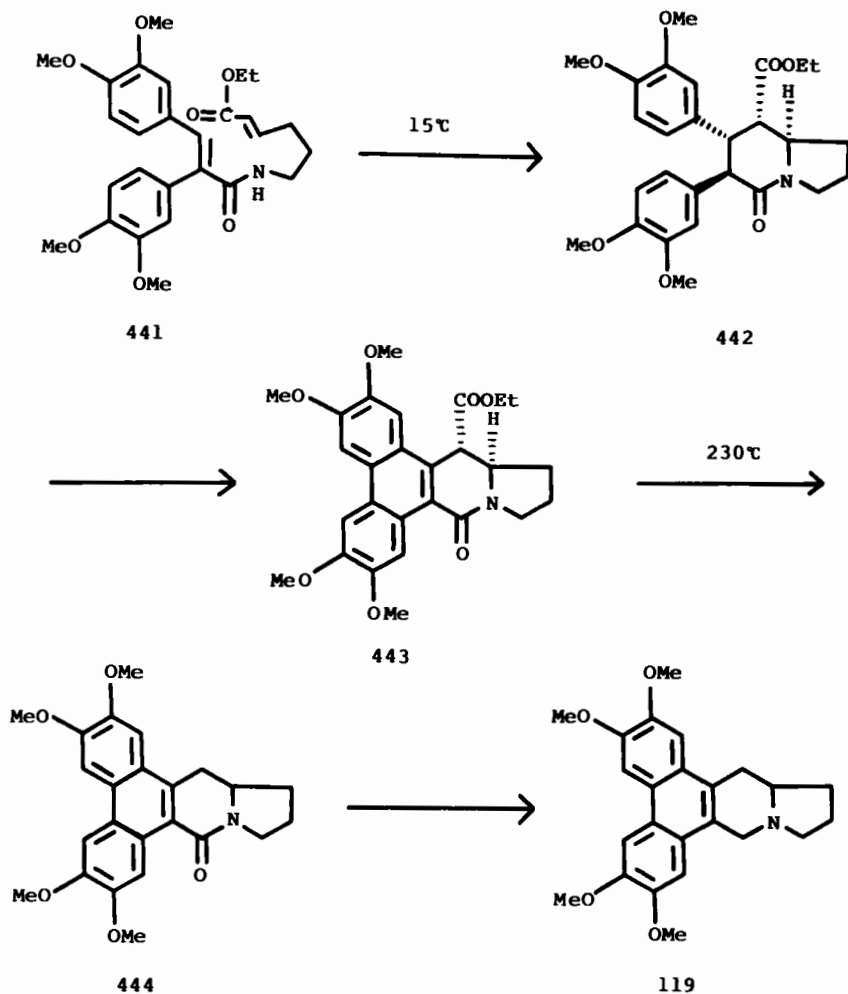
Kametani's group (84TL4541) discovered that the intramolecular cycloaddition of 1-azadienes prepared *in situ* from an enamide such as **435** provided a useful tool for the construction of quinolizidines and indolizidines. Heating enamides **435** and **437** in the presence of trimethylchlorosilane, triethylamine, and zinc chloride in toluene at 170–180°C in a sealed tube gave quinolizidines

**436** and **438** in 47% and 58% yield, respectively. They also applied this methodology to the synthesis of ( $\pm$ )-epilupinine (**139**) (Scheme 54) (85H1097). Heating enamide **439** in a similar method afforded lactam **440** in 56% yield. Lithium aluminum hydride reduction of **440** gave ( $\pm$ )-epilupinine (**139**).



SCHEME 54

Later, this cycloaddition reaction was improved by the pretreatment of the enamide ester with an equimolar amount of trialkylsilyl trifluoromethanesulfonate and triethylamine at ambient temperature. The synthesis of tyrophorine (**119**) was achieved by the above improved method (Scheme 55). The enamide ester **441** was subjected to annulation using *t*-butyldimethylsilyl triflate and triethylamine at 15°C to produce the bicyclic lactam **442** in 68% yield. Oxidation of **442** with thallium(III) trifluoroacetate and boron trifluoroetherate in a mixture of dichloromethane and trifluoroacetic acid at 4°C produced (83%) the pentacyclic compound **443**. Hydrolysis of **443**, followed by decarboxylation of the resultant acid, gave the pentacyclic lactam **444**. Reduction of **444** with sodium bis(2-methoxyethoxy)aluminum hydride in refluxing dioxane afforded tyrophorine (**119**) (85CC1159).



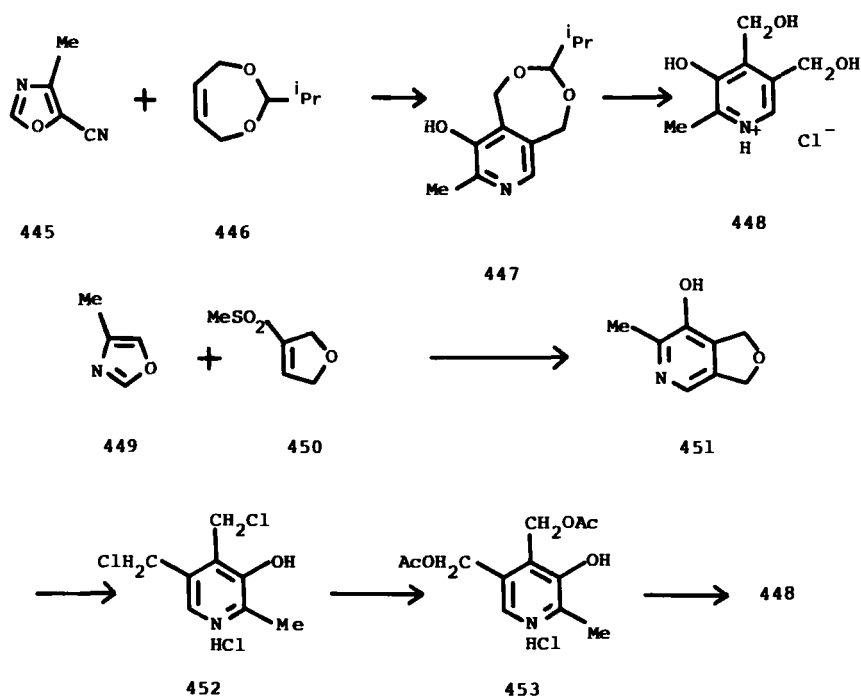
SCHEME 55

## B. 2-AZADIENE SYSTEMS ( $C=NC=C$ )

### 1. Intermolecular Cycloaddition Reactions

In 1957, Kondrat'va described the first example of a Diels–Alder cycloaddition of an oxazole with an alkene to produce pyridine (57MI1). This methodology was used extensively up to 1974 in the synthesis of pyridine and pyridine derivatives (69RCR540; 74AHC(17)99; 75CRV389; 81MI1; 83T2869). In 1975 (75MI1) and in 1979 (79LA1657), two groups established

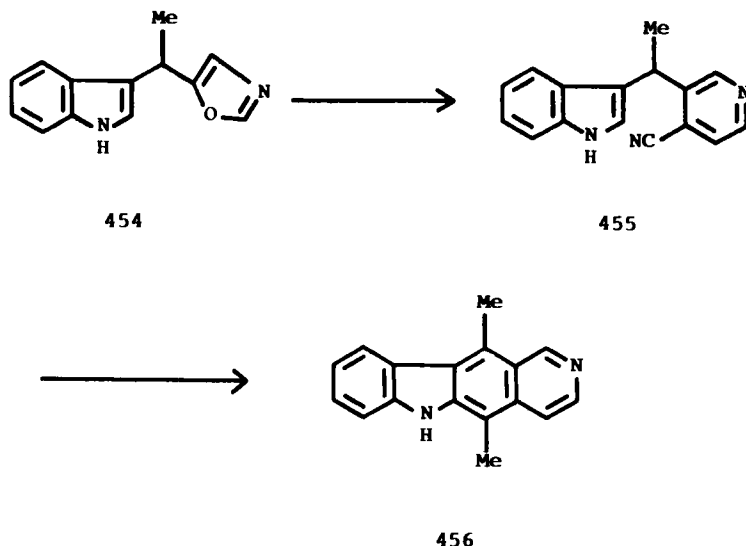
the synthesis of pyridoxine (**448**) via intermolecular cycloaddition using oxazoles and suitable alkenes (Scheme 56). Reaction of cyanomethyloxazole (**445**) with cyclic acetal **446** gave the corresponding pyridine derivative (**447**). Hydrolysis of the acetal afforded pyridoxine (**448**) in a two-step sequence (75MI1). However, Diels–Alder reaction of oxazole **449** with vinylsulfone **450** afforded dihydrofuroypyridine (**451**) (80%). Hydrolysis with hydrochloric acid followed by treatment with acetic anhydride gave diacetate **453**, which was further hydrolyzed to pyridoxine (**448**) (79LA1657).



SCHEME 56

Kozikowski and Hasan (77JOC2039) used an intermolecular Diels–Alder reaction for the synthesis of the pyridocarbazole alkaloid ellipticine (**456**) (Scheme 57). Reaction of oxazolidiene **454** with excess acetic acid at 145°C gave the pyridine **455** in 16% yield. Addition of methyllithium to cyanopyridine **455** followed by hydrolysis and cyclization with acetic acid afforded ellipticine (**456**).

It is well known that Diels–Alder reaction of oxazoles as azadienes with acetylenic dienophiles result in the formation of furan derivatives via elimination of a nitrile from the adduct in a retro Diels–Alder process

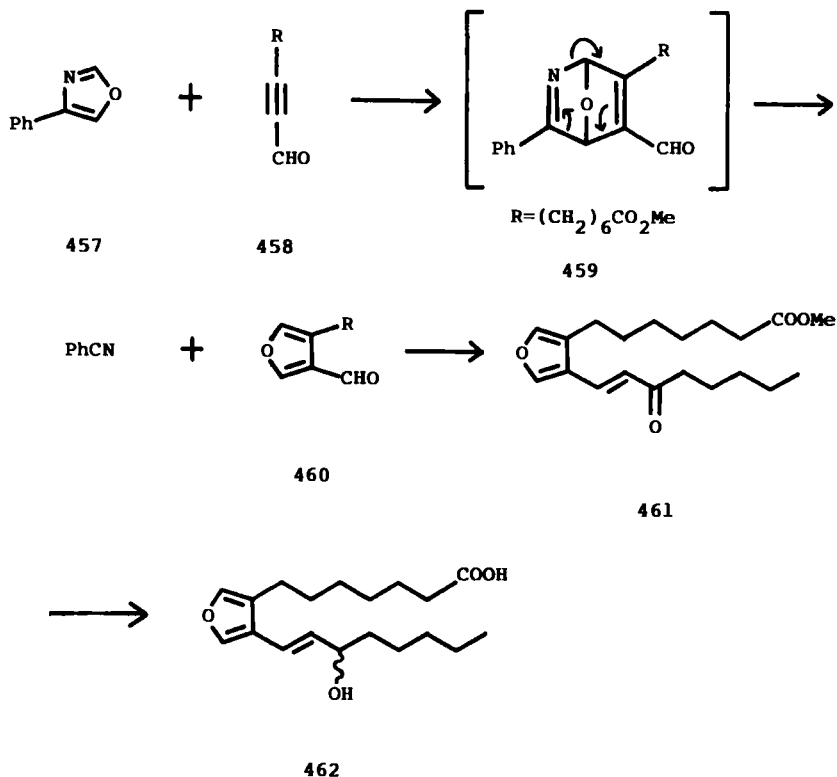


SCHEME 57

(81MI1). Ansell's group (81TL1727) has synthesized the furan prostanoid (**462**) by this Diels–Alder and retro Diels–Alder route (Scheme 58). Thus, heating acetylenic aldehyde **458** with an excess of oxazole **457** at 200°C gave 3,4-disubstituted furan **460** (73%). Treatment of **460** with dimethyl 2-oxoheptylphosphonate under usual conditions gave the enone **461**, which, after ketone reduction followed by ester hydrolysis, afforded the PGH<sub>1</sub> analogue **462**.

Bradsher and others (74AHC(16)289; 75JOC1195; 79JOC4680; 82JCS(P1)249) have established that cycloaddition of isoquinolinium salts with electron-rich alkenes is virtually 100% regioselective and, for easily polarizable, unsymmetrical alkenes, highly stereospecific.

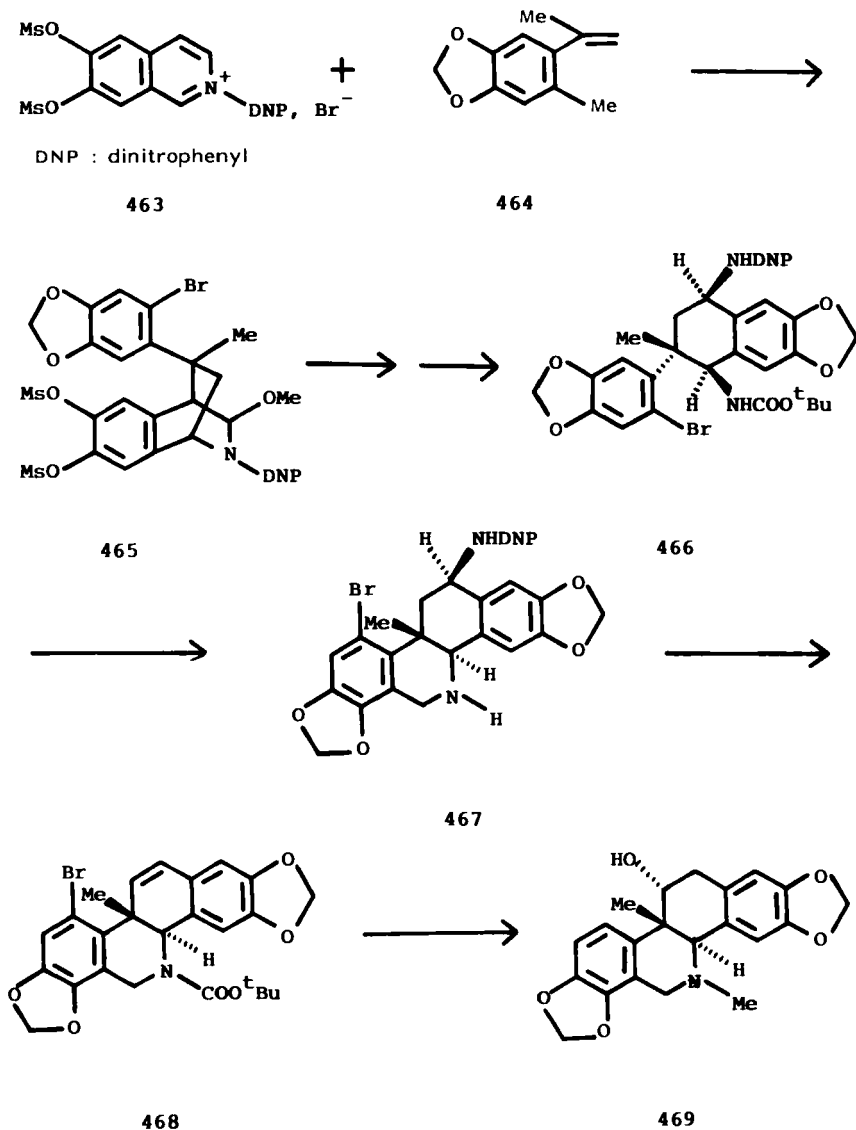
Falck and Manna (83JA631) investigated this reaction for the synthesis of benzophenanthridine alkaloids ( $\pm$ )-epicorynoline (**469**) (Scheme 59) and *O*-methylarnottiamide (**475**) (Scheme 60). Treatment of  $\alpha$ -methylstyrene **464** with 2,4-dinitrophenyl (DNP) isoquinolinium salt in methanol/dichloromethane in the presence of powdered calcium carbonate generated isomerically pure adduct **465** in 70–75% yield. Adduct **465** was transformed into urethane **466** by hydrolytic cleavage, Jones oxidation, and diphenylphosphoryl azide-mediated Curtius rearrangement. Selective saponification and catechol bisalkylation by the procedure of Eschenmoser (71AG(E)330) afforded compound **466**. Acidic hydrolysis of urethane in **466** followed by Pictet–Spengler cyclization generated the B/C *trans*-fused benzophenanthridine **467**. After *N*-ethoxycarbonylation, exhaustive methylation of the tertiary amine, and



SCHEME 58

Hofmann degradation, styrene **468** was formed. Epoxidation of **468** with *m*-chloroperbenzoic acid from the less hindered side and lithium aluminum hydride reduction gave ( $\pm$ )-epicorynoline (**469**). Moreover, slow addition of the  $\alpha$ -methoxystyrene **471** to isoquinolinium salt **470** gave cycloadduct **472** in 90% yield. The adduct was hydrolyzed by acid and the resultant aldehyde oxidized to naphthoic acid by Jones oxidation. Modified Curtius rearrangement of **473** with added benzyl alcohol afforded benzyl urethane **474**, which was reduced by lithium aluminum hydride and formylated with chloral to give *O*-methylarnottiamide (**475**) (Scheme 60).

Neunhoeffer and Wiley (78HC226) discovered that 1,2,4-triazine served as a reactive, electron-deficient diene in inverse electron demand Diels–Alder reactions with electron-rich or strained olefins. Cycloaddition occurs exclusively across C-3/C-6 of the triazine nucleus and there is a strong preference for the nucleophilic carbon of the dienophile to be attached to C-3

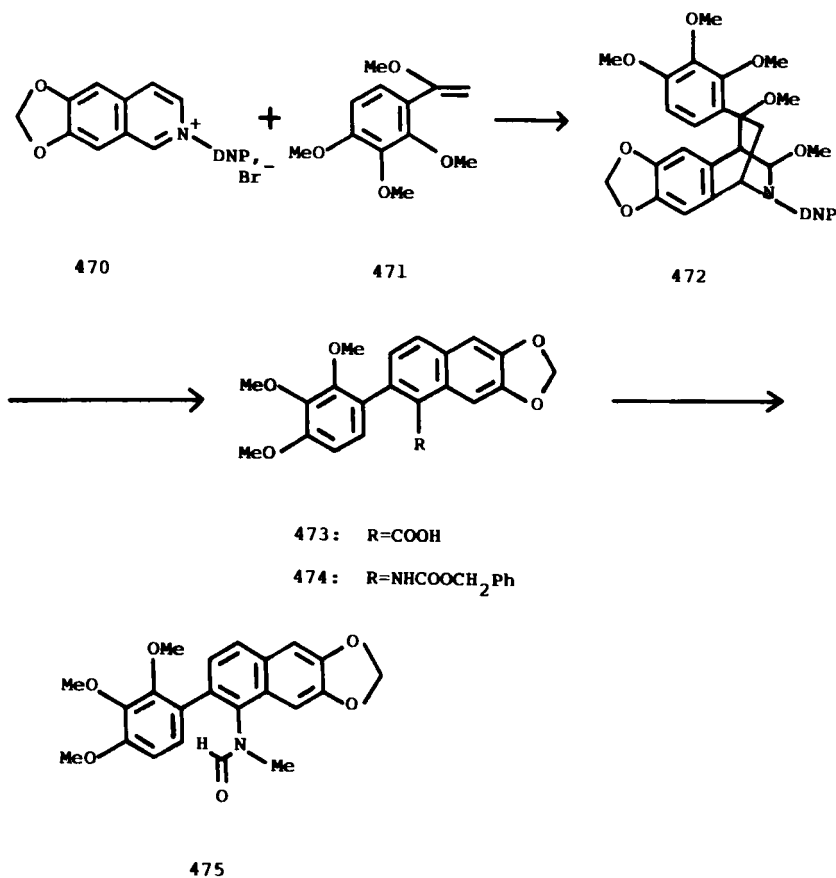


SCHEME 59

of the 1,2,4-triazine. Many examples have been described in an excellent review (83T2869).

Boger and others (82JOC3761; 82JOC3763; 83JOC623; 85JA5754) used this pyridine annulation for the formal total synthesis of antitumor, antibiotic streptonigrin (63) by an intermolecular Diels–Alder reaction between 1,2,4-

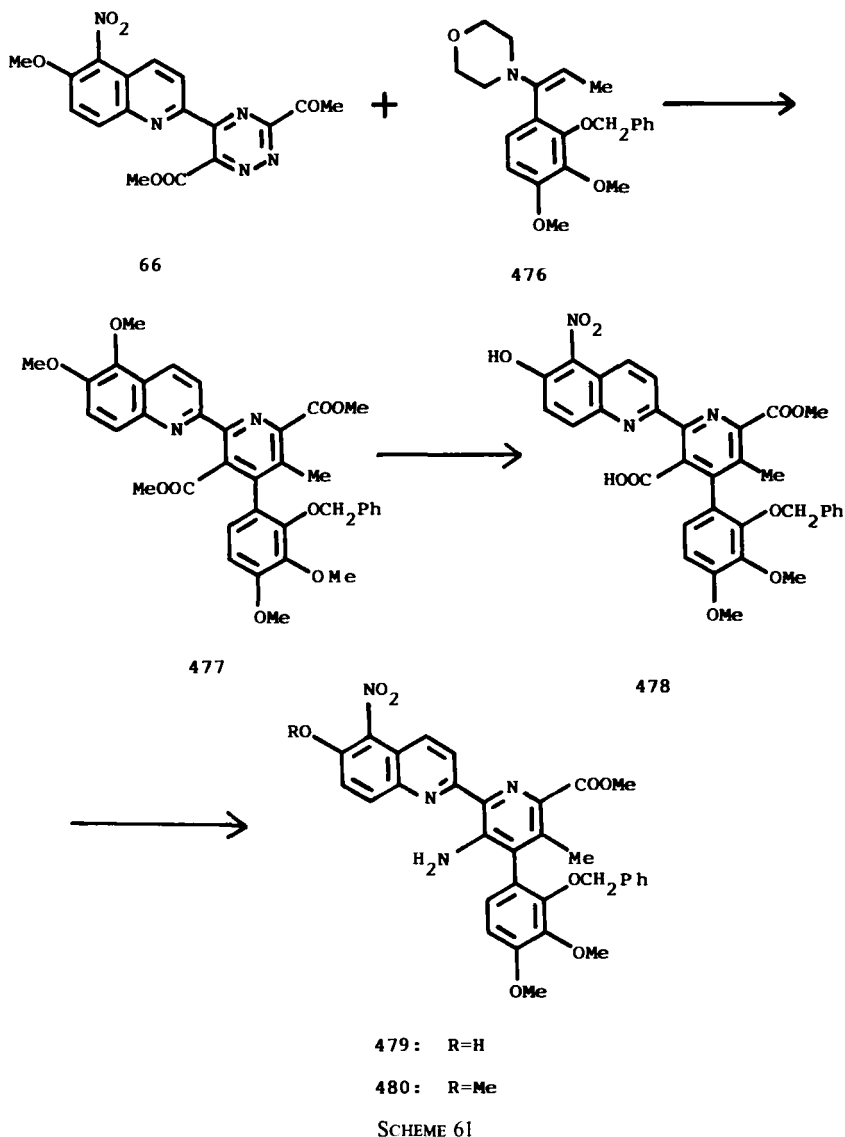




SCHEME 60

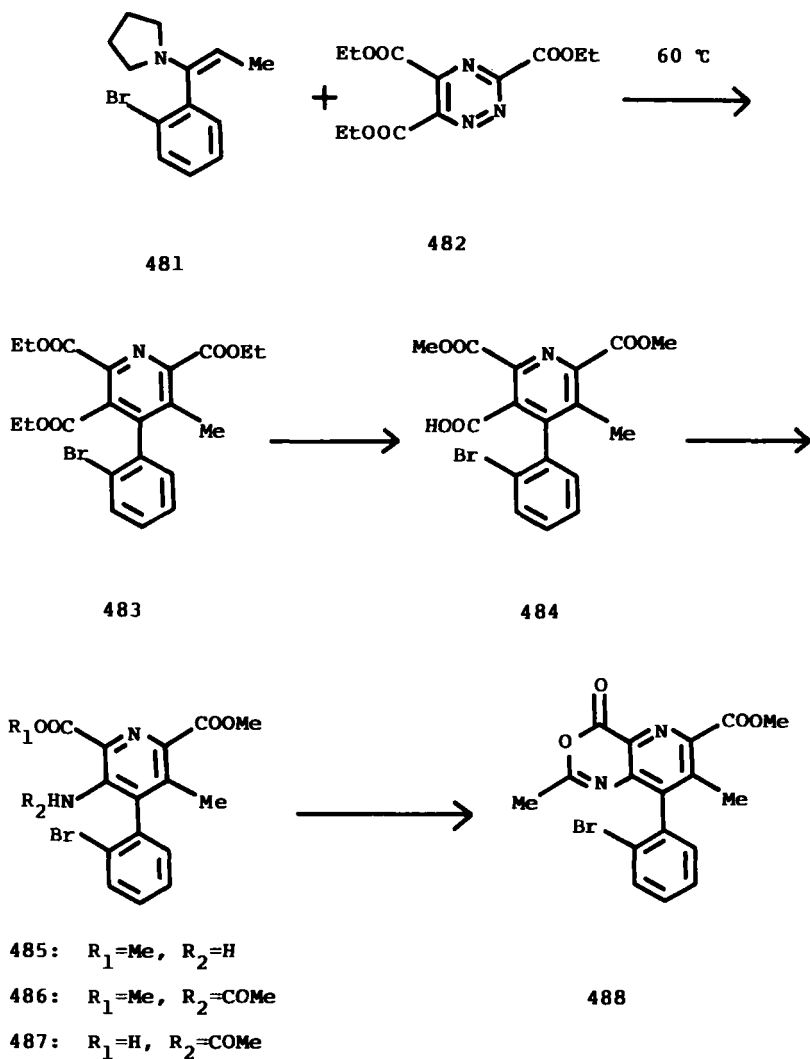
triazine **66** and enamine **476**. The pressure-promoted cycloaddition (6.2 kbar, 25°C) of triazine **66** described in Section II,A,1 and enamine **476** provided the desired adduct **477** and its regioisomer (2.8:1) in 65% yield. Treatment of tetracyclic compound **477** with the sodium salt of phenylselenenol followed by esterification of the unhindered carboxylic acid afforded **478**. Conversion of the 5-carboxylate to an amine using a modified Curtius rearrangement followed by methylation of the free phenol **479** provided known tetracyclic amine **480** (Scheme 61).

Boger's group (84TL3175; 85JOC5782; 85JOC5790) extended this synthetic methodology to the related antitumor antibiotic lavendamycin (**496**), as shown in Scheme 62. Inverse electron demand Diels–Alder reaction of enamine **481** in methylene chloride at 25°C gave the 4-phenylpyridine **483** and

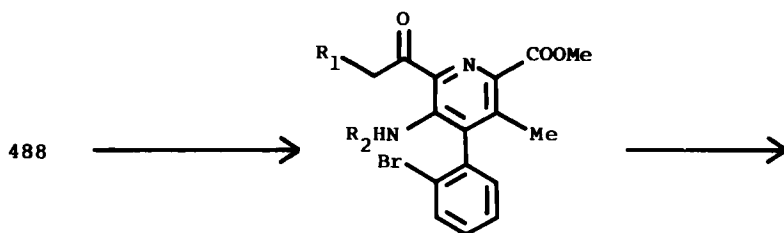


its regioisomer (7.5:1) in 50% yield. Exhaustive ester hydrolysis of triester **483** to the triacid followed by selective esterification of the two hindered carboxylic acids afforded the dimethyl ester **484**. Modified Curtius rearrangement of the mono acid **484** gave the desired aromatic amine **485**. After acetylation of amine **485**, base-catalyzed ring closure of **486** to the oxazinone **488** followed by aqueous workup afforded **487**. Reclosure of **487** to the

oxazinone **488** by dicyclohexylcarbodiimide (DCC) followed by treatment with  $\alpha$ -lithiomethyl phenylsulfoxide and subsequent reductive desulfurization of the  $\beta$ -keto sulfoxide **489** yielded **490**. Selective amide hydrolysis and subsequent palladium(0)-promoted closure of **491** provided the  $\beta$ -carboline moiety of lavendamycin (**492**). Friedländer condensation of  $\beta$ -carboline **493** gave pentacyclic compound **494**. Debenzylation of **494** followed by oxidation with Fremy's salt provided known bromoquinoline-5,8-dione **495**.

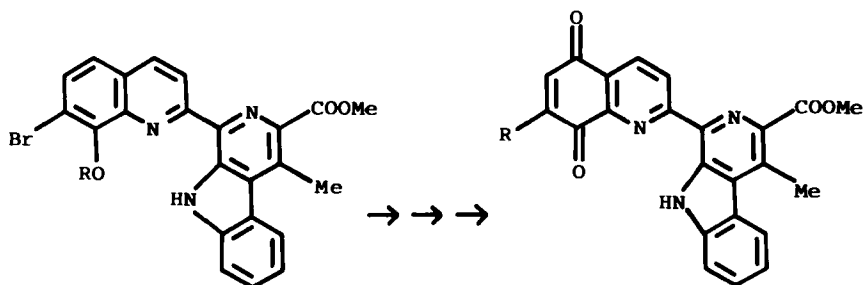
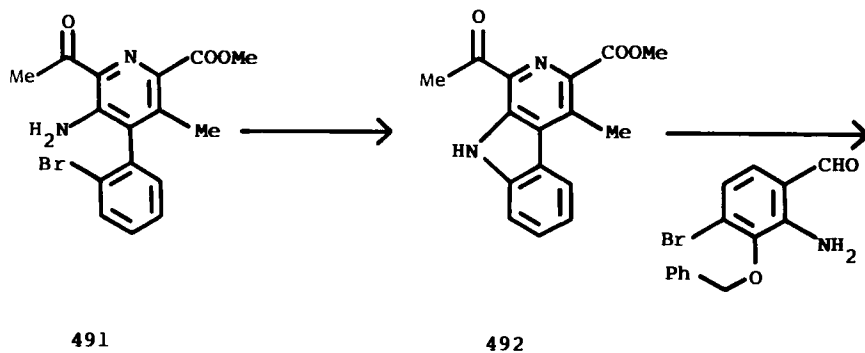


SCHEME 62



489:  $R_1 = \text{SOPh}$ ,  $R_2 = \text{Ac}$

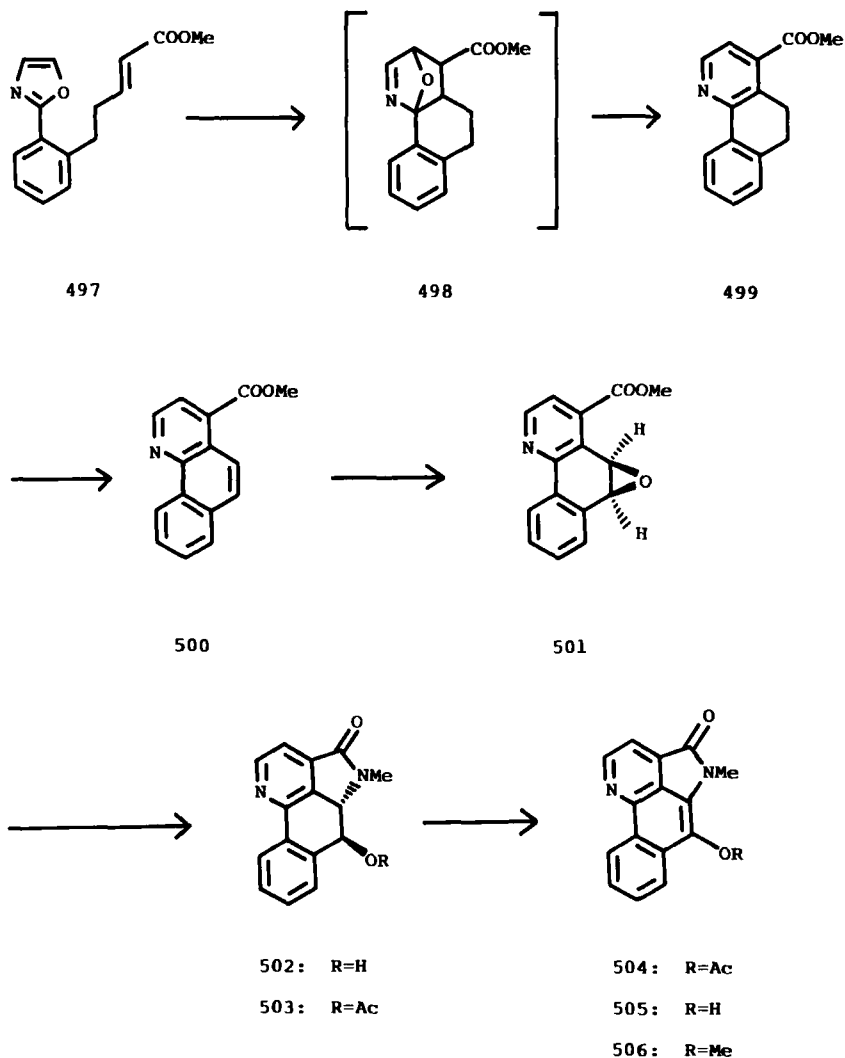
490:  $R_1 = \text{H}$ ,  $R_2 = \text{Ac}$



SCHEME 62 (continued).

## 2. Intramolecular Cycloaddition Reactions

An intramolecular Diels–Alder reaction of oxazoles with alkenes has not been investigated (83T2869). Recently, Levin and Weinreb (83JA1397; 84JOC4325) applied an intramolecular Kondrat'va pyridine synthesis (74AHC(17)99; 81MI1) to the total synthesis of azaphenanthrene alkaloids eupolauramine (**506**). Independently, some examples of intramolecular

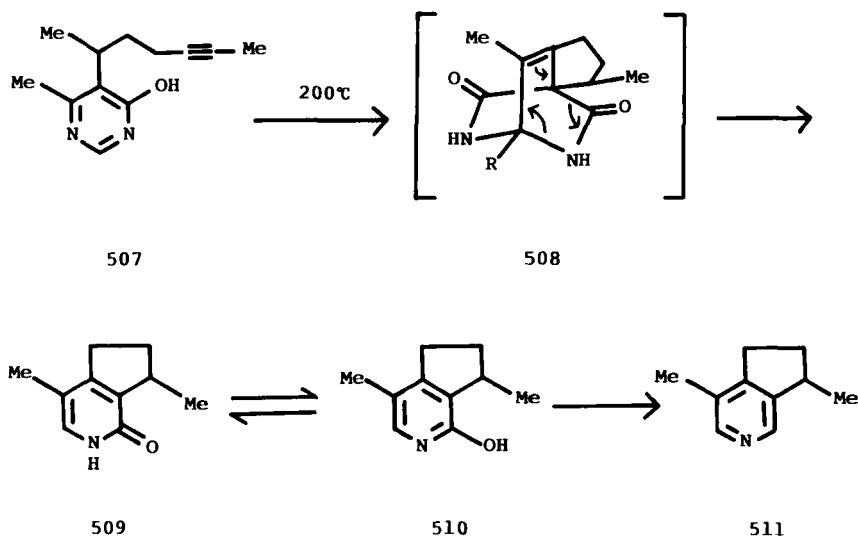


SCHEME 63

alkene-oxazole cycloadditions to give pyridines have appeared (83CPB4247). Heating Diels-Alder precursor **497** in *o*-dichlorobenzene for 16 hr in the presence of DBN afforded the tricyclic pyridine **499** (76%) through the cycloadduct **498**. Dehydrogenation of **499** with *N*-bromosuccinimide gave the azaphenanthrene **500**. Oxidation of ester **500** with sodium hypochlorite under phase-transfer conditions gave azaarene epoxide **501**. Treatment of epoxide **501** with dimethylaluminum *N*-methylamide followed by acetylation of the resulting alcohol **502** provided acetate **503**. Oxidation of **503** with *N*-bromosuccinimide gave acetyldemethyleupolauramine (**504**). Hydrolysis of ester **504** with potassium hydroxide formed a phenoxide anion which was directly quenched with dimethyl sulfate to give eupolauramine (**506**) (Scheme 63).

Sammes and his group (77JCS(P1)663; 78JCS(P1)1293; 81JCS(P1)1909) attempted the thermal intramolecular cycloaddition of the substituted pyrimidine **507** possessing an alkyne to produce a monoterpene alkaloid ( $\pm$ )-actinidine (**511**) (Scheme 64). Upon thermolysis of the pyrimidine **507** at 200°C in a sealed tube, using dimethylformamide as solvent, intramolecular cycloaddition led to the known pyridone **509** in 87% yield by the loss of the amide bridge from intermediate **508**. Conversion of the pyridone **509** into the chloropyridine followed by reductive dechlorination afforded racemic actinidine **511**.

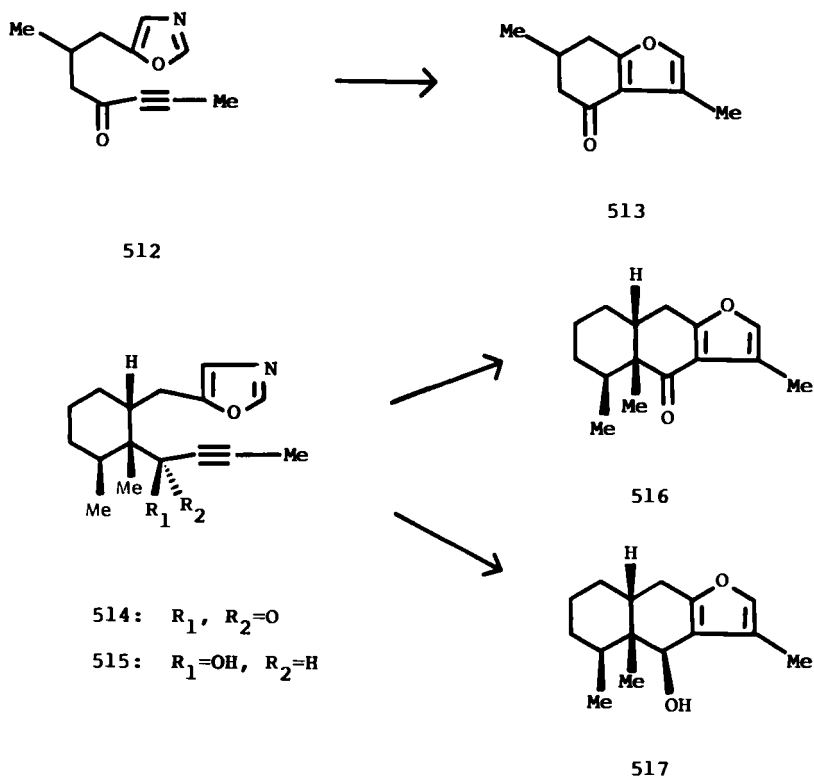
On the other hand, Jacobi and Walker (78JA7748) established in 1978 that the intramolecular variant of the well-known reaction (81MI1) of oxazoles



SCHEME 64

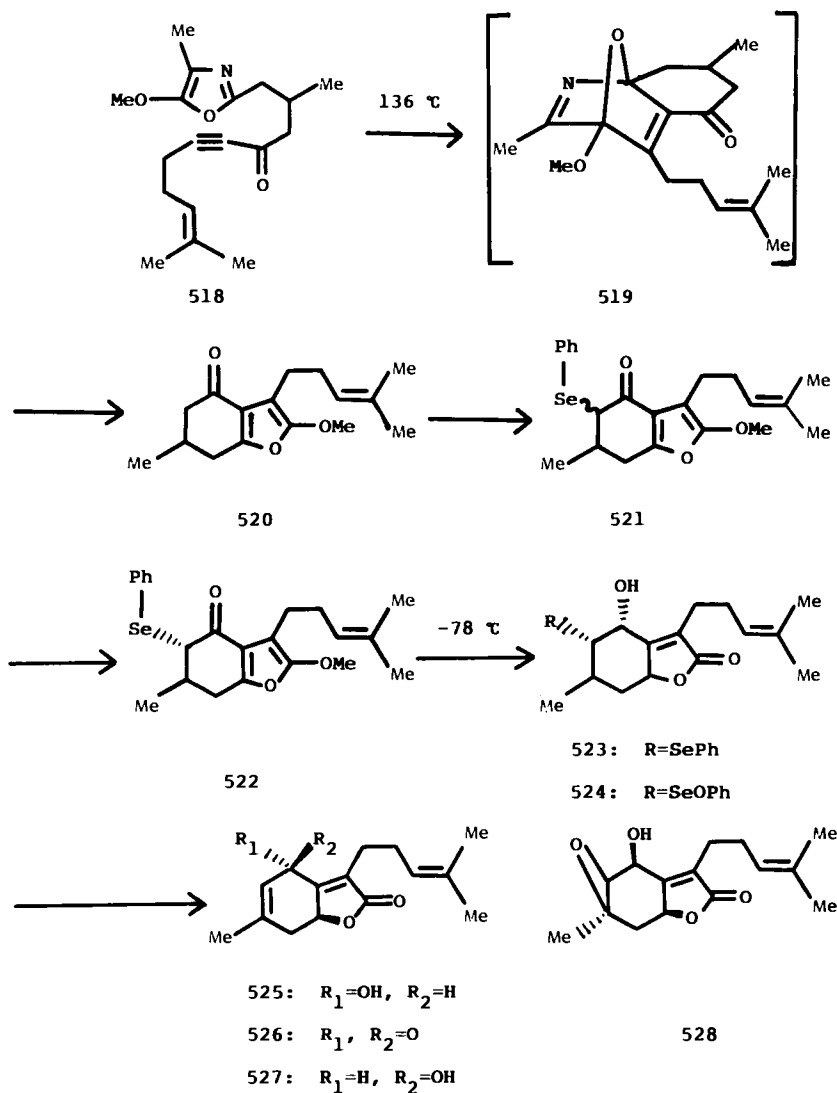
with acetylenic dienophiles is effective in the synthesis of the highly oxygenated members of the sesquiterpene class. First, they offered a new route to evodone (**513**), the simplest member of the naturally occurring furanoterpenes (Scheme 65) (81JOC2065). Heating a solution of acetylenic oxazole **512** in ethylbenzene under hydroquinone catalysis in the absence of light gave the expected evodone **513** in 76% yield. Similarly, Jacobi's group (81JA4611; 84JA5585) achieved the total synthesis of furanoeremophilans ( $\pm$ )-ligularone (**516**) (84%) and ( $\pm$ )-petaselin (**517**) (92%) based on the intramolecular Diels–Alder reaction of acetylenic oxazoles **514** and **515**, respectively.

Jacobi extended this methodology for the synthesis of the novel sesquiterpene ( $\pm$ )-paniculide A (**528**) (Scheme 66) (84TL4859). Thermal cycloaddition of **518** in ethylbenzene in a similar condition afforded the methoxyfuran **520** in 94% yield through the intermediate **519**. Phenylselenation of **520** with LDA and phenylselenenyl chloride gave a 1:1 mixture of phenylselenides **521**, which upon kinetic deprotonation–protonation afforded the  $\alpha$ -isomer (**522**) in



SCHEME 65

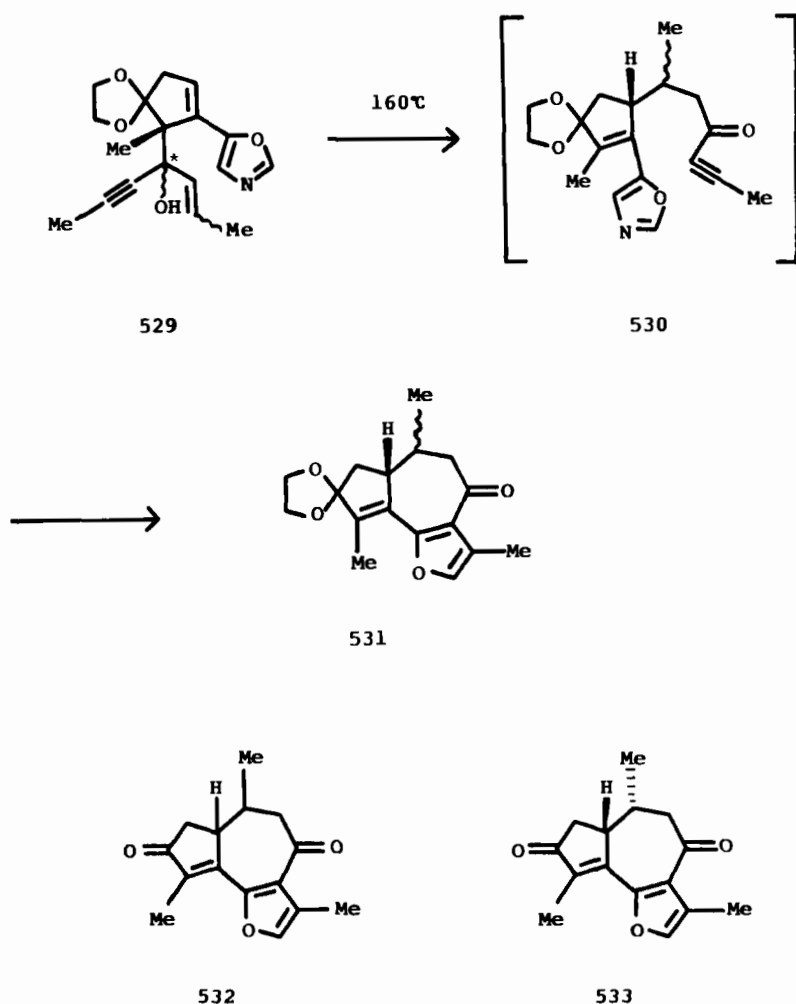
a 96:4 ratio. Reduction of **522** with diisobutylaluminum hydride gave the  $\alpha$ -alcohol, which, without isolation, was hydrolyzed at pH 5 to afford butenolide **523**. Oxidation of **523** with sodium metaperiodate followed by heating in toluene in the presence of sodium carbonate provided alkene **525**. Oxidation of **525** to ketone **526** followed by reduction with Luche's procedure (78JA2226) afforded the known alcoholic butenolide **527** exclusively.



SCHEME 66



Furthermore, Jacobi and Selnik (84JA3041) have elegantly achieved the total synthesis of ( $\pm$ )-gnidine (**532**) and ( $\pm$ )-isognidine (**533**) via sequential oxy-Cope rearrangement, hetero Diels–Alder, and retro Diels–Alder reactions. The first examples of this methodology are illustrated in Scheme 67. Thermolysis of **529** at 160°C gave the ketal **531** ( $\beta$  and  $\alpha$ -Me) via Cope intermediate **530** ( $\beta$  and  $\alpha$ -Me), which upon mild acid hydrolysis afforded gnididine (**532**) and isognididine (**533**) in 45 and 57% yields, respectively.

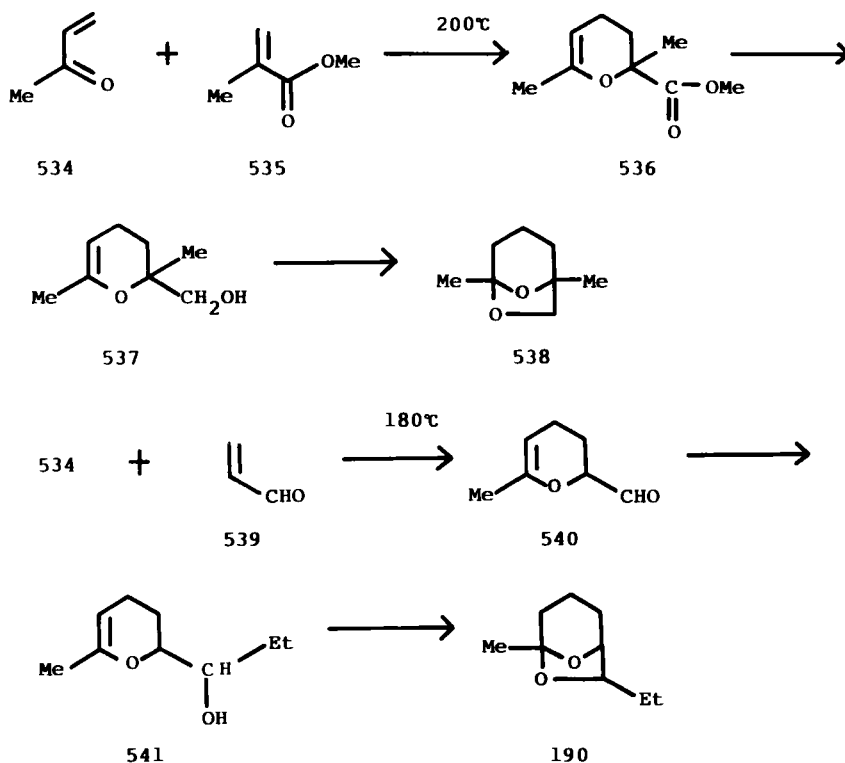


SCHEME 67

C. 1-OXADIENE SYSTEMS ( $O=C-C=C$ )

## 1. Intermolecular Cycloaddition Reactions

The well-known Diels–Alder reactions of  $\alpha,\beta$ -unsaturated carbonyl compounds show interesting features from a synthetic point of view (75CRV651). In earlier studies, an intermediate dihydropyran, obtained by a hetero Diels–Alder reaction, was utilized in the synthesis of frontaline (538) (51JA5270; 71JOC2390), brevicomin (190) (71JOC2390), valerianine (546), and adaline (550) (73BSB699). A synthesis of 4-methyl-2,8-dioxabicyclo[3.3.1]octane (21%) was reported in 1951 based on a Diels–Alder reaction of metallyl alcohol and acrolein (51JA5270). Mundy improved this work in 1971 (Scheme 68). A Diels–Alder reaction of methyl vinyl ketone (534) with methyl methacrylate (535) afforded cycloadduct 536 in 67% yield. Lithium aluminum hydride reduction of 536 gave alcohol 537, which was cyclized by mercuric acetate to frontaline (538). Similarly, the Diels–Alder reaction of methyl vinyl

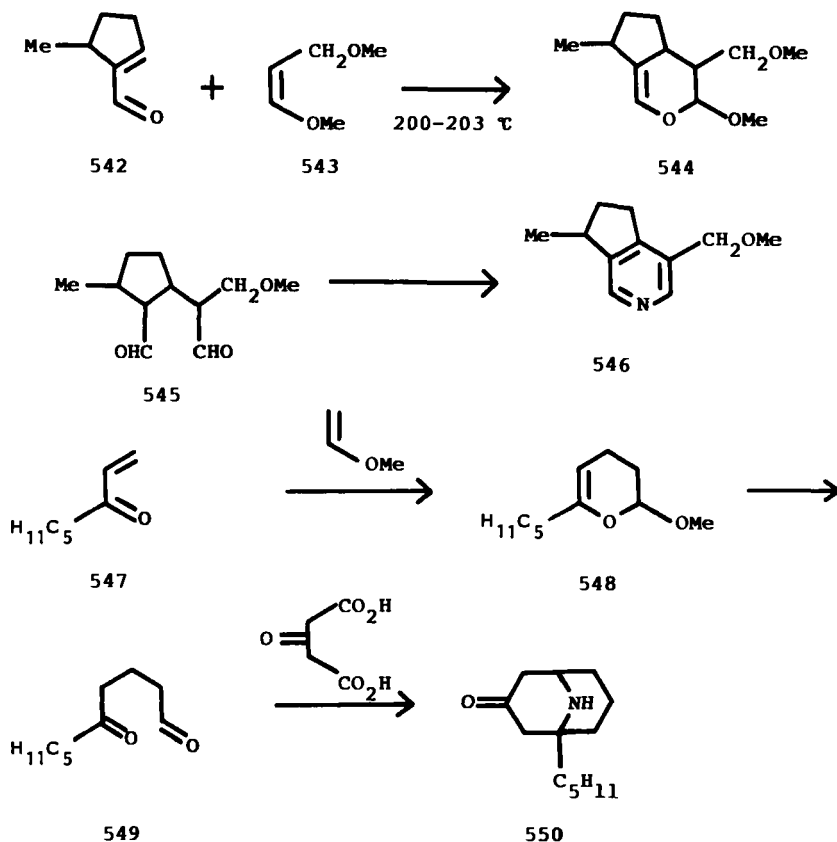


SCHEME 68

ketone (**534**) with acrolein (**539**) gave the adduct **540**. Treatment with ethylmagnesium bromide followed by cyclization afforded brevicomin (**190**) (Scheme 68).

Valerianine (**546**), a monoterpene alkaloid, was synthesized by using a Diels–Alder cycloaddition of heterodiene **542** with enol ether **543** (Scheme 69) (70AG(E)891). Heating cyclopentenecarbaldehyde **542** with the enol ether at 200–203°C afforded a 47% yield of the dihydropyranyl ether **544**, which consisted of three diastereomers. Hydrolysis of the ether **544** with acid gave iridodial (**545**), which was condensed with a nitrogen source to afford racemic valerianine (**546**).

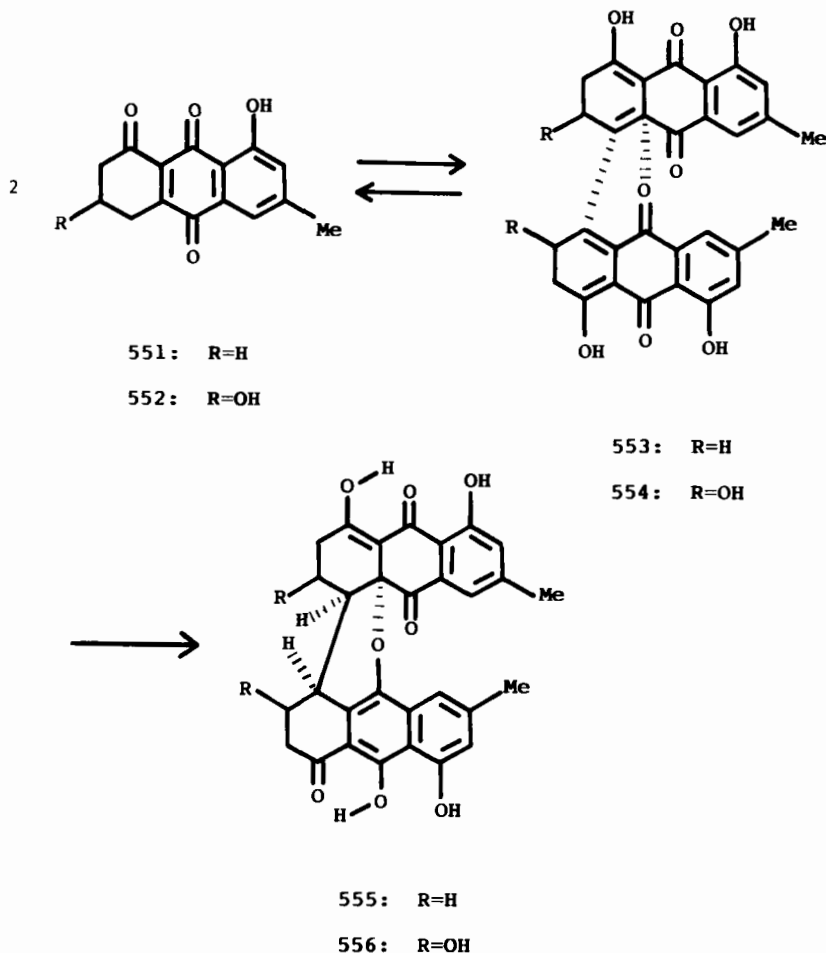
A total synthesis of adaline (**550**) has been performed (73BSB699). The vinyl ketone **547** was submitted to hetero Diels–Alder reaction with methyl vinyl ether to yield the dihydropyran derivative **548** in 60% yield. Acid hydrolysis of **548** produced the keto aldehyde **549**. Finally, a Mannich reaction involving



SCHEME 69

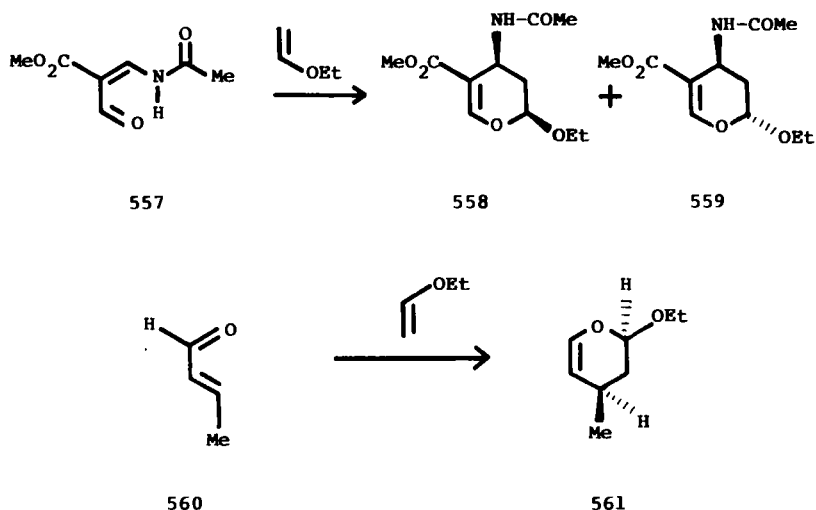
**549**, ketoglutaric acid, and ammonium chloride led to racemic adaline (**550**) (Scheme 69).

For the structure determination of flavoskyrin (**556**), a yellow metabolite of *Penicillium islandicum*, a biosynthetic pathway involving Diels–Alder cycloaddition (Scheme 70) has been proposed by Shibata and co-workers (73T3721). The dimerization of 1-oxo-1,2,3,4-tetrahydroanthraquinone derivative **551** has been elucidated by intermolecular Diels–Alder reaction with exo approach of the monomers in the model experiment as formulated in **553**. Eventually, an enolized form of tetrahydroemodin (**552**) was considered as a monomeric precursor which could be dimerized by the intermolecular Diels–Alder reaction to form flavoskyrin (**556**).



SCHEME 70

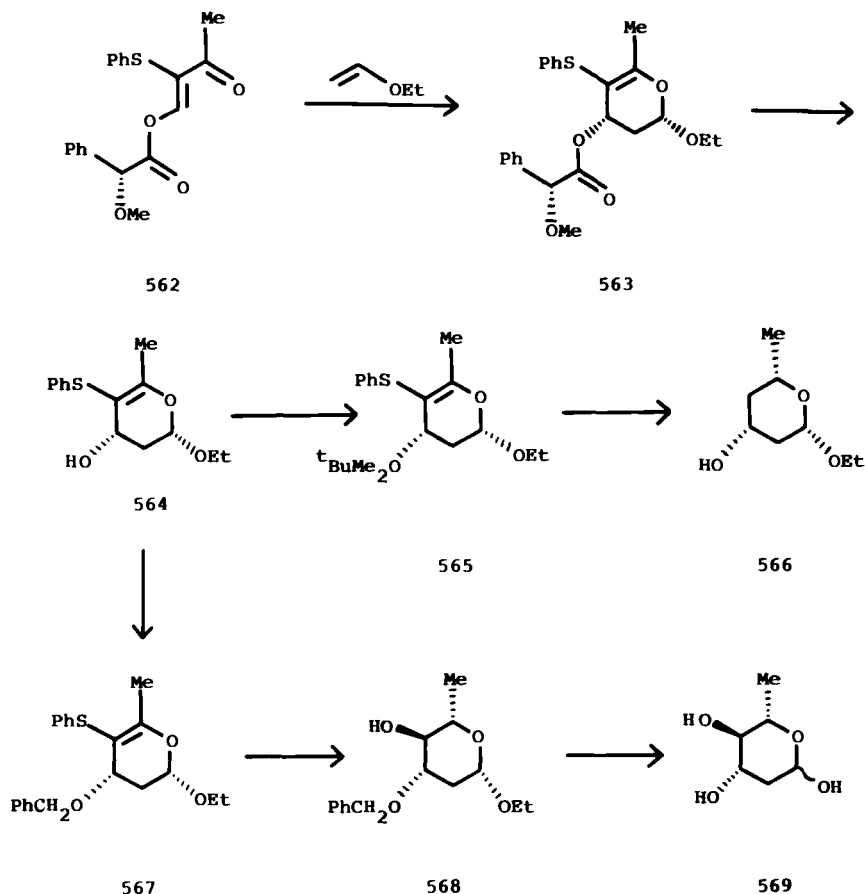
The groups of Tietze (82AQ793; 82TL1147; 83AG901; 85TL5273), Snider (79JA6023; 80TLL133), and Danishefsky (84TL721) have independently investigated the intermolecular Diels–Alder reaction of  $\alpha,\beta$ -unsaturated compounds with enol ethers that served as an approach to several natural products such as carbohydrates. Tietze demonstrated that the cycloadditions are regioselective, and, with respect to the configuration of the enol ether employed, also stereoselective. However, the reaction always produces two diastereomers. For example (85TL5273), a hetero Diels–Alder reaction of *N*-acyl enaminecarbaldehyde **557** with ethyl vinyl ether at 90°C afforded a 1:1.9 mixture of pyran derivatives **558** and **559** in 93% yield (Scheme 71). On the other hand, Danishefsky reported that the cycloaddition of crotonaldehyde (**560**) with ethyl vinyl ether under catalysis of  $\text{Yb}(\text{fod})_3$  at room temperature gave the dihydropyran **561** (60–80%) stereospecifically (Scheme 71).



SCHEME 71

Schmidt and Maier (82TL1789; 85TL2065) developed the highly successful hexopyranose synthesis based on a hetero Diels–Alder reaction along with an endo-specific diastereoface-selective addition as shown in Scheme 72. The Diels–Alder reaction of the chiral heterodiene **562** with ethyl vinyl ether at room temperature afforded (+)-**563** and its diastereomer (ratio 2:1, 60% yield). Deacylation gave the corresponding alcohol **564**, which was converted to the *O*-silylated compound (+)-**565** or *O*-benzyl ether (+)-**567**, respectively. Raney Ni treatment of (+)-**565** led to removal of the phenylthio group and to diastereospecific hydrogenation of the double bond affording after desilylation 2,4,6-trideoxy- $\beta$ -(+)-hexopyranoside **566**. Desulfurization of (+)-

**567** with Raney Ni followed by hydroboration with diborane dimethylsulfide, after oxidative workup, gave olivose derivative **568**. Hydrogenolitic debenzylolation and acidic cleavage of the glycosidic bond gave (–)-L-olivose (**569**) (2,6-dideoxy-L-arabinohexose).

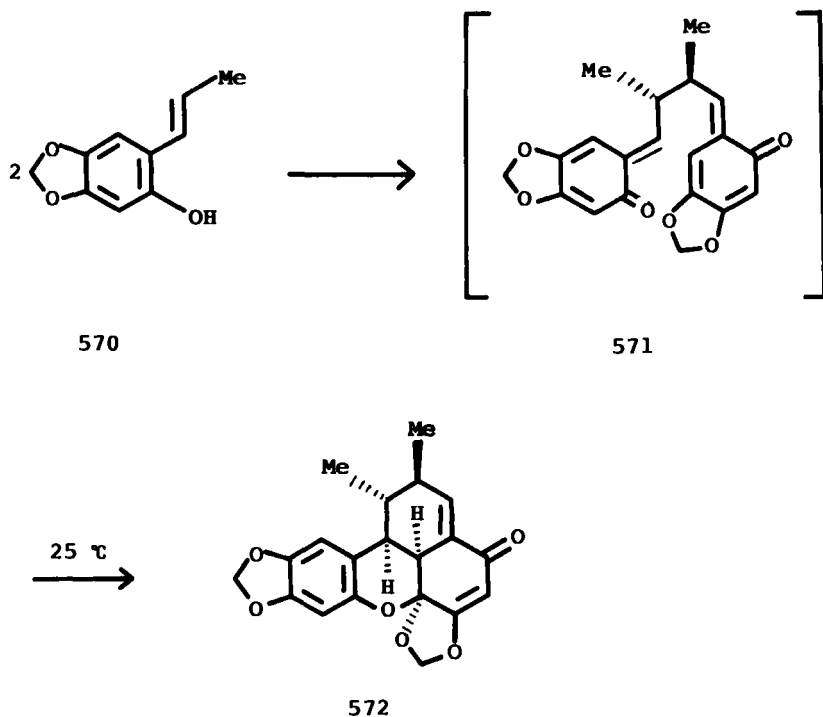


SCHEME 72

## 2. Intramolecular Cycloaddition Reactions

Reactivity and stereoselectivity in the intramolecular cycloaddition of certain electron-deficient heterodiene systems have been well established by Tietze's group (80AG(E)134; 81TL219; 82AG(E)863; 82TL51) and Takano *et al.* (85H41). In 1971, Chapman *et al.* (71JA6696) encountered an elegant biomimetic synthesis of carpanone (**572**), a lignan from bark of the carpano

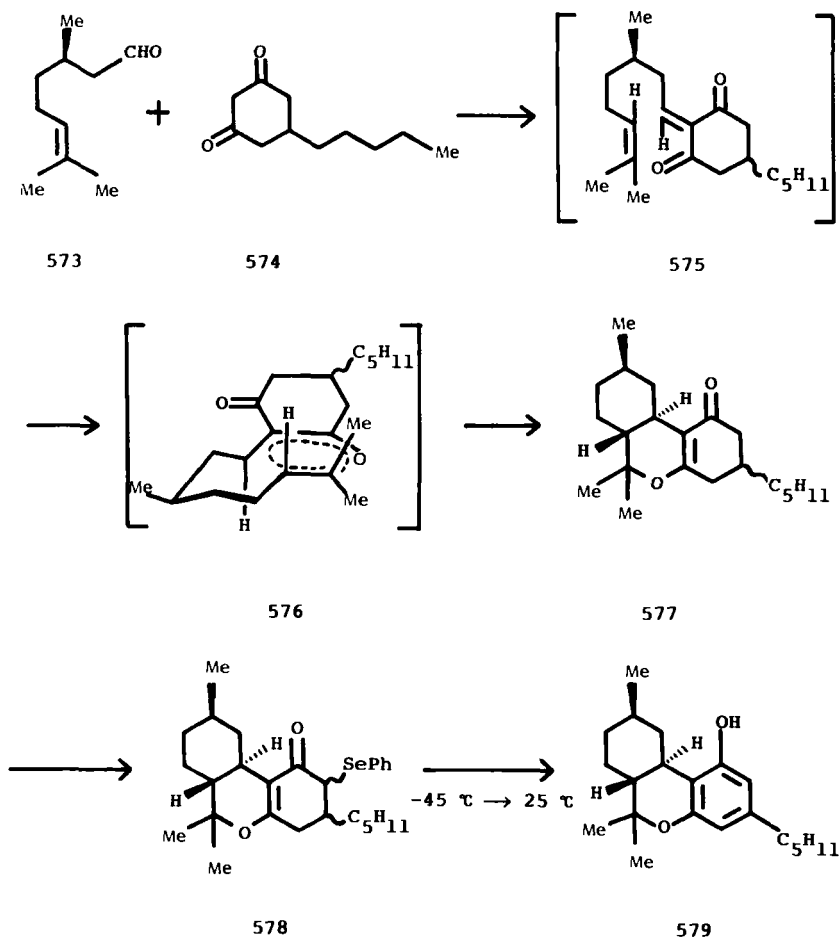
tree. The phenolic coupling of 2-(*trans*-1-propenyl)-4,5-methylenedioxyphenol (**570**) with palladium chloride gave the intermediate bis(quinodimethide) **571**. Spontaneous intramolecular Diels–Alder reaction of **571** afforded carpanone (**572**) in 46% yield. This sequence is characterized by remarkable control over five chiral centers (Scheme 73).



SCHEME 73

Tietze's group (82AG(E)221) utilized this intramolecular version in the highly stereoselective synthesis of unnatural (–)-(9*R*)-hexahydrocannabinol (**579**) (Scheme 74). Condensation of (*R*)-citronellal (**573**) with cyclohexa-1,3-dione **574** at 100°C gave about a 1:2 mixture of both tricyclic pyran **577** through the intermediate **575** and the transition state **576** (65%). The mixture of adduct **577** was treated with LDA and converted into the selenide **578** by phenylselenenyl chloride. Oxidation of **578** with *m*-chloroperbenzoic acid at –40°C to the selenium oxide and subsequent warming to 25°C afforded (–)-(9*R*)-hexahydrocannabinol (**579**) via syn elimination and a 1,5-hydrogen shift.

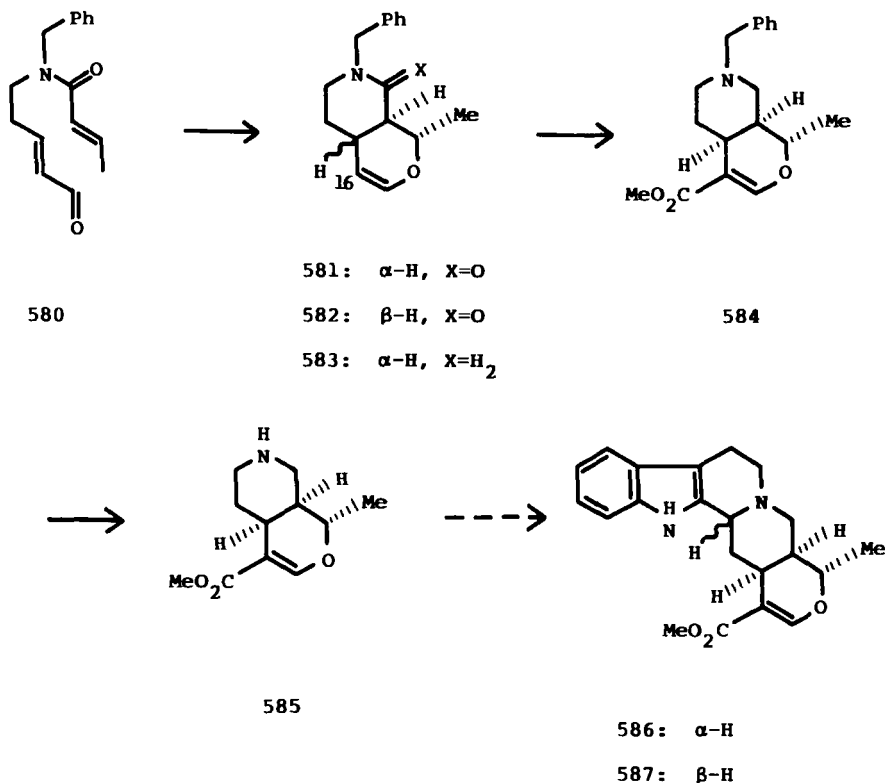
Facile and formal syntheses of the yohimbine alkaloids tetrahydroalstonine (**586**) and akuamigine (**587**) have been reported by Martin (84TL4863)



SCHEME 74

(Scheme 75). The D/E ring system of these alkaloids has been constructed by the intramolecular  $[4 + 2]$ -cycloaddition of an oxadiene with an  $\alpha, \beta$ -unsaturated amide. Thermolysis of the diene **580** at  $190^{\circ}\text{C}$  in xylene produced a 4.5:1 mixture of the *cis* and *trans*-cycloadducts **581** and **582**, respectively. They could be separated to provide *cis*-lactam (73%). Subsequent hydride reduction of **581** with aluminum hydride produced the tertiary amine **583**. Acylation of **583** with trichloroacetyl chloride followed by a haloform cleavage gave the ester **584**. Finally, hydrogenolysis of the *N*-benzyl group provided the known bicyclic amine **585**, which was previously converted to a mixture of **586** and **587**.





SCHEME 75

#### IV. Conclusion

This article summarizes recent advances in the synthesis of natural products by hetero Diels–Alder cycloaddition reactions up to 1985. These recent disclosures have had a great impact on heterocyclic natural product syntheses.

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- |            |   |
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# Mass Spectral Techniques in Heterocyclic Chemistry: Applications and Stereochemical Considerations in Carbohydrates and Other Oxygen Heterocycles<sup>1</sup>

J. R. JOCELYN PARÉ

*Centre de Recherches Alimentaires de Saint-Hyacinthe (C.R.A.S.H.),  
3600 boul. Casavant Ouest,  
Saint-Hyacinthe,  
Canada J2S 8E3*

KRZYSZTOF JANKOWSKI

*FESR, Université de Moncton, Moncton,  
New Brunswick, Canada E1A 3E9*

JOHN W. APSIMON

*Department of Chemistry, Carleton University,  
Ottawa, Ontario, Canada K1S 5B6*

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## I. Stereochemical Considerations in Mass Spectrometry

Mass spectrometry has evolved to one of the organic chemist's most powerful tools for structure elucidation. The basic ionization form (electron impact, EI) involves the bombardment of gas-phase molecules by an electron beam which is energetic enough (nominally 70 eV) to ionize and induce a series of unimolecular fragmentations. Despite the excess energy imparted by this electron beam, several structural features of the neutral molecules are often retained in the decomposing molecular ions, thus enabling deduction of some structural information from the fragmentation pattern.

In early stages of mass spectrometry it was shown that limited stereochemical information could be obtained from certain systems under electron impact ionization conditions (49JCP358); (62MI1); (63MI1); (64MI1). Despite these early reports, statements repeatedly appeared in the literature to the effect that mass spectrometry was insensitive to configurational differences. More recently, however, four reviews, which appeared in 1968 (68OMS659), 1976 (76TS35), 1977 (77M1), and 1983 (83MSR233), attracted more interest to the potential of this technique in stereochemical studies.

Selected topics related to stereochemical studies in mass spectrometry, such as heterocyclic compounds (78CHE1169), hydrocarbons (80MI1), ionization and appearance energy correlations (79MI1), and the connection of electron impact phenomena with free radical chemistry (80T2687), have been the subject of recent reviews.

From these previous references, it can be seen that to date there exists no unified theory to account for the stereochemically related effects encountered in mass spectrometry. It is possible, however, to view these as being the result of two main considerations: thermochemical and kinetic correlations (83MSR223).

Under the heading of thermochemical correlations we find discussion topics such as correlation between the molecular ion-radical  $[M^{+\cdot}]$  and its configuration, the inverse correlation of abundance of  $[M - R]^+$  ions with enthalpy (and its direct counterpart), and its ionization and appearance energy correlations (63AMS370; 63NL(197)284); 63NL(200)881; 66BSB668; 69OMS603; 69OMS1257; 71OMS705; 71OMS763; 72IZV209; 72OMS533;

74AMS105; 75OMS1067; 76CJC3206; 76OMS675; 77JA6500; 78JA2959; 78JA3005; 78MI1; 78MI2; 81IZV1809). Unfortunately these data are not always accessible for oxygenated heterocycles such as oligosaccharides thus reducing greatly their analytical usefulness.

Under the heading "Kinetic Correlations," however, we can find terms and topics much more common to the practicing organic chemist. In fact, several stereoisomeric systems show significant differences in the abundance of some of their fragment ions. These differences cannot be explained in terms of thermochemical considerations alone. For example, the mass spectra of several *cis* diones exhibit retro Diels–Alder (RDA) fragment ions as their most abundant ions (73JA4244). These ions are not found in the mass spectra of the corresponding *trans* isomers. In the same vein, molecular ions are most abundant in the *trans*, but of much lower abundance in the *cis*. The difference in the enthalpies of formation of these isomers is too small to account for the extremely different fragmentation behavior observed under EI conditions (83MSR223) (e.g., see Fig. 1a). Another example is that of the methyl esters of

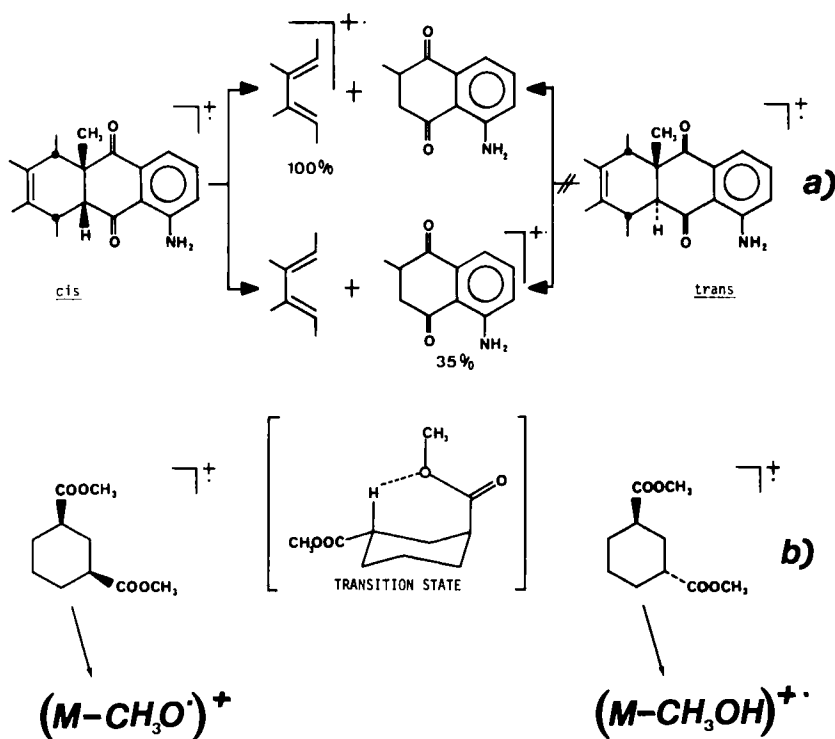


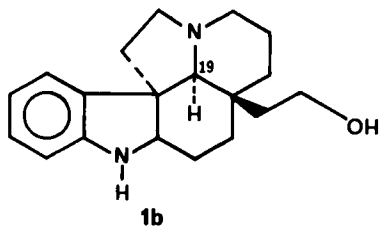
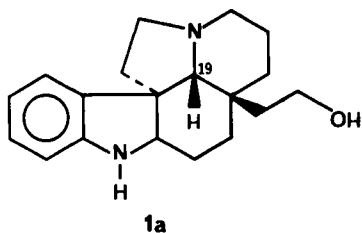
FIG. 1. Examples of kinetically controlled stereochemical effects on fragmentation pathways in mass spectrometry.

cyclohexane-1,3-dicarboxylic acids (Fig. 1b). The *cis*-diester loses a  $\text{CH}_3\text{O}\cdot$  radical from its molecular ion, while the *trans* isomer mainly eliminates methanol (80MI2). Here again the significant difference in the fragmentation patterns cannot be explained on the basis of relative stability arguments.

In these and in many other systems, kinetic considerations provide a way to explain stereospecific fragmentation processes detected by mass spectrometry. It is expected that there should be a difference between stereoisomers in the accessibility of transition states for fragmentation processes that involve bond formation (e.g., rearrangements or elimination of neutral molecules) or the concerted rupture of several bonds. This situation leads to different energies of activation of specific fragmentations for particular stereoisomers, resulting in different fragmentation patterns. Differences in the magnitude of frequency factors operating in certain fragmentation processes of stereoisomers may also lead to different mass spectra. This effect has been isolated in only one case (72OMS235), but it may be of importance in many systems. This finding underlines the importance of structural features of the transition states in the fragmentation of gas-phase ions, a fact that has been neglected in several theoretical treatments. The accessibility of cyclic transition states based on the configuration of the stereoisomers in the ground state is of great value in the prediction of stereospecificity of fragmentation processes involving a transfer of specific atoms or groups. This is believed to be true for the dicarboxylates presented in Fig. 1b, where the cyclic transition state shown is available only for the *trans* isomer. Such anchimeric assistance has been shown to operate in certain systems, enhancing some fragmentation processes in stereoisomers having suitable configurational features (65JOC2886; 66JA3881; 66JOC3120; 69OMS919; 71OMS705; 73OMS1287; 76T2735; 77MI1; 78JA8021; 78MI3).

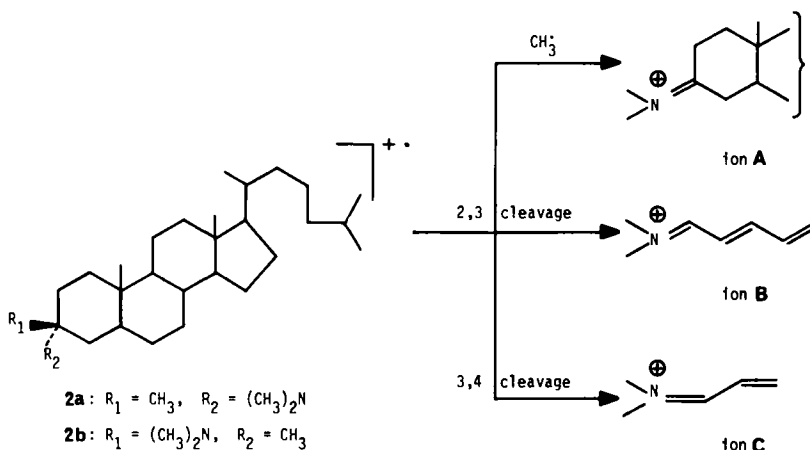
Cycloreversion reactions such as RDA (e.g., Fig. 1a) can also be explained in terms of kinetic correlations through the arguments that RDA must happen via a one-step mechanism; it is really the retro-replica (in the gas phase) of the thermal Diels–Alder reaction performed in solution (73JA4244; 74AMS25; 75TH1; 77JA3432; 78TH1). Fragmentation patterns of other systems, such as steroidal skeletons, have also been shown to be influenced by the stereochemistry of the molecular ion-radical (63BSF1971; 65T1855; 67CC50).

One of the early reported cases of different mass spectra of stereoisomers was that of deacylcyclindrocopol **1a** and its epimer at C-19, **1b** (63TL1731; 64MI1). The much more pronounced loss of a hydrogen radical from the molecular ion radical of **1b** ( $[\text{M} - \text{H}]^+$ , 10.6 versus 1.7% for **1a**) was attributed to the assistance of the anti electron pair on the adjacent nitrogen atom. Deuterium labeling at C-19 showed that the hydrogen was indeed lost from that position (63TL1731). A similar argument was used to explain the difference between the abundance of  $[\text{M} - \text{H}]^+$  ions of epimeric quinolizines (63JOC2831).



The relatively easy elimination of axial anomeric groups in glycosides may also be a demonstration of a similar stereoelectronic effect (66MI1; 74OMS480).

An interesting case is provided by the mass spectra of the epimeric 3-dimethylamino-3-methylcholestanes (**2**) (74OMS480). The molecular ion of **2a** loses a methyl radical to give ion **A** to a greater extent than does its epimer **2b** (100 and 37%, respectively), but gives rise to lower abundances of ions **B** and **C** whose formation is initiated by ring cleavage at bonds 2–3 and 3–4 (see **2**). These results suggest that the conformation of the amino group plays a role in the fragmentation, so that the activation energy for breaking a given C—C bond adjacent to the nitrogen is lowered when the  $n$  orbital of the nitrogen atom is antiparallel to that bond. The populations of the three gauche conformations of **2a** (axial dimethylamino group) are presumably unequal, and the highly populated one favors elimination of the  $\alpha$ -methyl radical. An equal abundance is expected for the gauche conformations of the isomeric **2b**, and consequently no preference is predicted for the loss of  $\text{CH}_3\cdot$  over the rupture of the other  $\alpha$ -bonds (78MI5).

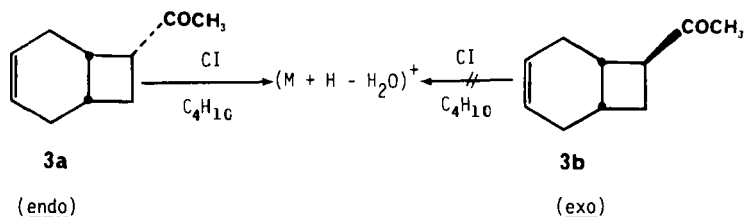


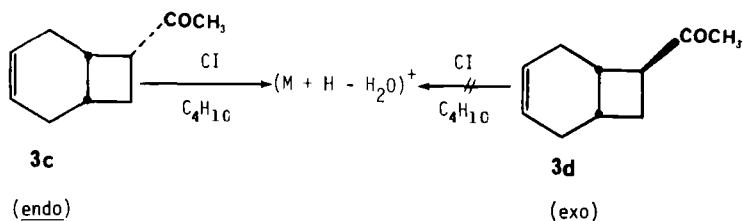
This stereoelectronic effect may explain other cases of different mass spectra of stereoisomers. The more pronounced loss of axial versus equatorial methyl groups in heteroatom-containing decalin systems, which has been attributed

to stability factors (69OMS1257; 71OMS763; 72IZV209; 72OMS533; 76OMS675), could also be interpreted in terms of a stereoelectronic effect, namely lower energy of activation in isomers in which the  $n$  orbital of the heteroatom is antiparallel to the bond to be broken.

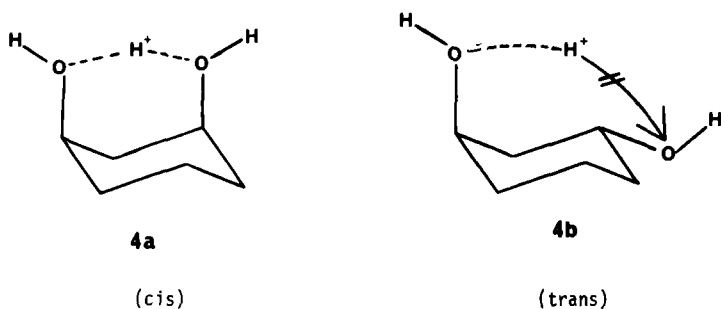
The most frequently reported stereospecific fragmentations are those involving new bond formation via cyclic transition states. These processes include the elimination of neutral HX molecules ( $X = OH, RO, RCOO, Cl, R$ ) and various more complicated fragmentations involving hydrogen migrations. The elimination of neutral HX has been covered extensively in reviews (68OMS659; 76TS35; 77MI1). Figure 1b shows a related case. A common feature of these processes is the proximity of the migrating hydrogen to its destination in the parent molecule. This simple relationship between structure and stereospecificity in these elimination processes gives them some predictability (73JA2387; 76TS35; 77MI1; 79HCA1040; 79HCA1065; 82OMS269). On the other hand, it should be emphasized that a necessary condition for stereospecificity is that the stereoisomeric molecular ions do not undergo isomerization to a common structure prior to fragmentation; such isomerizations are very difficult to predict.

The first case of a pronounced effect of configuration on the behavior of stereoisomers under chemical ionization (CI) conditions was reported in 1972 (72OMS765; 74OMS49). 3-Oxo-5- $\alpha$ -steroids give rise to most abundant  $[M + H]^+$  ions, while the most prominent peaks in the CI mass spectra of the 5- $\beta$ -isomers are due to the elimination of water:  $[M + H - H_2O]^+$ , 100%;  $[M + H - 2H_2O]^+$ , 90%. This rather large difference between the stereoisomers was more prominent when a high energy gas ( $H_2$ ) was used over a less energetic one ( $CH_4$ ). The greater extent of the  $H_2O$  elimination in the *cis*-A/B isomers was explained by the short distance between the C-3 oxygen and the C-9 hydrogen atoms (72OMS235). A similar explanation was suggested for the abundant  $[M + H - H_2O]^+$  ions detected in the CI (isobutane) mass spectra of some unsaturated endo-bicyclic ketones, but not in their *exo* isomers (74JOC1752; 76JOC136). An allylic hydrogen atom is accessible to the carbonyl oxygen only in the *endo* ketones, resulting in an efficient loss of water from these isomers (74JOC1752; 76JOC136) (see structures 3 for example).





An interesting general feature was discovered in 1974 in the CI mass spectra of stereoisomeric cyclic 1,3- and 1,4-diols (74T2971). The abundance of the  $[\text{M} + \text{H}]^+$  ions is often significantly higher for cis than for trans diols, while the trans isomers yield relatively more abundant  $[\text{M} - \text{H}]^+$  and  $[\text{M} + \text{H} - \text{H}_2\text{O}]^+$  ions. This behavior is explained by the stabilization of the  $[\text{M} + \text{H}]^+$  ions by an intramolecular proton bridging which is possible only in the cis diols (74T2971) (see structures **4** for an example of a pair of cyclic 1,3-diols). This effect was found in various alicyclic and acyclic diols (76OMS219; 77OMS566; 77ZN(B)810; 79JA3685; 80OMS160; 81OMS37), and in other difunctional compounds (77OMS200; 77OMS531; 77ZN(B)573; 78IZV2015; 80BMS413; 80OMS249; 81JCS(P2)1591; 82OMS265; 82OMS277). Configurational assignments were made in some substituted bicyclo[3.2.0]heptanes using this relationship (77JCS(P1)2349; 77T2433). Intramolecular ion solvation effects (79JA3658) and negative CI characteristics were also investigated (78JA6779).



Chemical ionization mass spectrometry is a powerful technique for conformational analysis of 2-amino alcohols (79OMS414; 80OMS268). The extent of dehydration under CI–isobutane conditions in several amino alcohols with fixed conformation is dependent on the distance between the functional groups: It is greatest for maximal distance ( $O,N$ -dihedral angle  $180^\circ$ ) and practically disappears in compounds with the dihedral angle smaller than  $90^\circ$ .

This effect is interpreted in terms of intramolecular proton transfer in the  $[\text{M} + \text{H}]^+$  ions (79OMS414). It is claimed that the dehydration peak  $[\text{M} + \text{H} - \text{H}_2\text{O}]^+$  in the mass spectrum represents the  $[\text{M} + \text{H}]^+$  ions

decomposed after protonation of the hydroxyl moiety, and the  $[M + H]^+$  peak represents ions protonated on the amino group.

Fragment ions obtained by softer ionization techniques, such as field ionization or field desorption (73MI1; 74OMS1086; 79CB743; 81ABC1505; 81MI1), alkali atom attachment (80OMS240), negative ionization (78MI6), and negative chemical ionization (72OMS1171), in some cases may also exhibit a stereospecific behavior. Stereochemical effects have also been reported in some systems for the slow decomposition of metastable ions, both in the relative abundances of the relevant ions (71OMS147; 74JA3482; 75JOC511; 75OMS1067; 76MI1; 77MI2; 78MI3; 79BMS78; 79MI2; 81T2625; 82OMS451) and in the magnitude of the kinetic energy released in these metastable ion transitions (66BSB668; 81OMS465; 82OMS451). The retention of configuration in nondecomposing ions was demonstrated in several cases by different collisional activation (CA) spectra of stereoisomers (79NJC517; 80BMS127; 80OMS80). Stereospecificity in these systems serves as a reliable probe for the retention of configuration in the ions and as an indication of the mechanistic details of the fragmentation processes. An important outcome of the investigations described above is the fact that mass spectrometry has become an additional technique for configurational studies for the organic chemist. The high sensitivity of mass spectrometry and the possibility of its application in the investigation of complex mixtures by combination with various separation methods ensure extensive use of this technique in future stereochemical studies.

Few applications to carbohydrates have been made as yet in terms of stereochemical effects, although several intriguing (if not controversial) reports have appeared that discuss the sensitivity of field desorption (FD) mass spectra (FDMS) to differences in the anomeric configuration of monosaccharides (73OMS1103; 81ABC1505). A limited number of aromatic glycoside monosaccharides were studied by FDMS and apparently reproducible differences in relative ion abundance were noted, especially between the  $\alpha$ - and  $\beta$ -linked anomers of *p*-nitrophenyl glycosides. However, the data regarding actual absolute ion count values were not presented (equivalent sensitivity is expected for both anomers) thus leaving the doubt that the differences seen might be related to the (undescribed) normalization procedure used by those authors. There has been no work reported on similar studies involving glycosides with longer sugar chains, although it has been shown that under FD conditions, protonation occurs at the glycosidic bond (81LA683) thus enabling the glycoside to undergo hydrolysis, which in turn is stereoelectronically controlled (66MI1; 74OMS480).

Another promising field is the investigation of stereochemistry of gas-phase ion-molecule reactions. Steric effects have been reported in several cases (72AC974; 74AC1709; 74JA4028; 75AC689; 75JA3600; 76MI2; 76MI3;

76OMS140; 77AC1071). An interesting effect has been observed in the efficiency of formation of attachment ions  $[2M + H]^+$  of optical isomers of dialkyl tartrates by chemical ionization. The abundance of attachment ions consisting of two enantiomeric molecules ("meso ions") is lower than that of the  $[2M + H]^+$  ions in which both molecules have the same configuration. This was the first report of detection of chirality by mass spectrometry (77JA2339).

## II. Applications of Mass Spectrometry to the Characterization of Carbohydrates

Mass spectrometry has made significant contributions to structural problems in carbohydrate chemistry, usually by confirming the structure of saccharides separated by gas chromatography. Much research has evolved from techniques of derivatization to prepare carbohydrate materials for analysis providing us with methods capable of resolving several problems in this area (71MI1; 73MI2; 74MI1; 80MI3; 80MI4).

Strategies for sequence determination of polysaccharides usually involve the permethylation and some form of limited degradation of a family of oligomers. These heterogeneous mixtures are chromatographically separated and purified for further degradation and analysis by classical procedures to yield monosaccharide derivatives suitable for gas chromatography/mass spectrometry (GC/MS). Partial degradation frequently entails acetolysis (68B1843; 70MI1; 75MI2; 77MI3) or acid-catalyzed hydrolysis and is very sample specific (70MI1; 75MI2; 76MI4; 80MI5), requiring independent evaluation for each polysaccharide in order to determine an adequate distribution and maximum yield of oligomers. Systematic and reliable procedures have been developed over the years to extract monosaccharide linkage information based on the identification of the resultant permethylated, reduced, and acetylated alditol acetates (67ACS1801; 70AG(E)610). These procedures have been reviewed (73MI3; 78MI7) and are widely used. They are presented in Section II,A, under the heading *Electron Impact Studies*.

Variations of the permethylation approach have appeared that take advantage of instrumental and data system advancements. Improvements in sensitivity and specificity have been reported (81MI2) by using methane chemical ionization mass spectrometry and selected ion monitoring. Another important modification has been the use of capillary GC columns for improved chromatographic resolution. In this approach the permethylated oligosaccharide is degraded by methanolysis to the corresponding methyl glycosides, which are subsequently acetylated and identified by GC/MS (81MI3). The greater complexity of products due to the anomeric methyl



glycosides (compared with the alditol acetate procedure, in which single derivatives are obtained for each sugar) is offset by the improved chromatographic resolution and the smaller number of chemical manipulations. Although these procedures provide only glycosyl linkage data, considerable structural details can be obtained from saccharides when this information is combined with composition data and our current understanding of the usual nature of carbohydrate sequence arrays. This is especially the case for oligosaccharides of mammalian glycoproteins and glycolipids.

### A. ELECTRON IMPACT STUDIES

Mass spectrometry as commonly practiced uses EI most frequently as the ionization mode. Carbohydrate derivatives rarely give molecular ions EI spectra, although molecular weights may often be inferred from various fragment ions. Detailed structural information is best obtained from EI spectra. Softer methods of ionization, including chemical ionization using reagent gases such as isobutane (76JOC3425; 77MI4), field ionization and field desorption (74OMS903) may produce molecular or quasi-molecular ions and, in general, give much more abundant ions in the high-mass range (500–2000 daltons), but their simpler spectra provide less structural information. These methods could become of greater importance with the development of chromatographic methods for the fractionation of higher oligosaccharides (see later). At present, oligosaccharide derivatives of molecular weights up to 1000 daltons are convenient for mass spectral analysis, and derivatives of molecular weights of up to 2000 daltons have been reported for permethylated glycoconjugates, such as gangliosides (77MI5) and oligosaccharides containing glycopeptides from extensive proteolytic digestion of glycoproteins (78MI8).

Ballou and collaborators fractionated a polymer-homologous series of 3-O-methylmannose polysaccharides (71JBC6835) from *Mycobacterium smegmatis* into discrete compounds by high-pressure liquid chromatography (HPLC) (79JBC1972) and then examined the field desorption mass spectra of the unsubstituted compounds (81PNA1471). Quasi-molecular ions were observed up to  $m/z$  2500 for a tetradecasaccharide. The appearance of fragment ions from the cleavage of successive glycosyl bonds provided the basis for complete sequence determination up to the decasaccharide level.

In terms of thermal stability and ease of interpretation of spectra, permethylated compounds and tetramethylsilyl (TMS) ethers are the derivatives of choice for mass spectrometry. At present, the separation and characterization of volatile derivatives by combined GLC–mass spectrometry are widely used for di-, tri-, and some tetrasaccharides. However, the

resolution of mixtures in the trisaccharide range is not always very good. In general, higher oligosaccharides are separated as the parent compounds, and individually prepared derivatives are introduced into the mass spectrometer by direct insertion. With the increasing potential of HPLC for the separation of oligosaccharide derivatives and the availability of commercial instruments for combined HPLC–mass spectrometry, the mass spectral analysis of mixtures of high-molecular-weight carbohydrates will, doubtless, be extended in the near future.

The interpretation of the mass spectra of oligosaccharide derivatives follows the general principles that have been elaborated for simple cyclic and acyclic carbohydrates (66MI1; 74MI1).

Many methylated polysaccharides are much less soluble in hot than in cold aqueous solvents. Accordingly, it is usually convenient to carry out partial hydrolysis in an organic solvent such as formic acid and then to complete the hydrolysis in dilute aqueous acid. Partially methylated alditol acetates formed on reduction with sodium borohydride followed by acetylation are the most widely used derivatives for the characterization of methylated sugars. The mass spectra of these compounds are normally simple to interpret, with characteristic fragmentation patterns (74MI1). Molecular ions are not seen in EI spectra taken at 70 eV, but molecular weights can usually be obtained by extrapolation from fragment ions coupled with the use of GLC retention time data. Direct observation of molecular ions is frequently possible in chemical ionization mass spectra (77MI6).

Primary fragment ions from partially methylated alditol acetates (Fig. 2) arise by  $\beta$ -cleavage with, in general, preferred formation of:

1. Ions of lower molecular weight;
2. Ions from cleavage between two methoxyl-bearing carbon atoms, with no marked preference between the two possible methoxyl-bearing cations; and
3. Ions from cleavage between a methoxyl-bearing carbon atom and an acetoxyl-bearing carbon atom with a marked preference for the methoxyl-bearing species to carry the positive charge; but
4. Ions formed by scission between two acetoxyl-bearing carbon atoms are generally of low abundance.

There is little tendency for chain scission to take place adjacent to a deoxy-generated carbon atom (i.e., cleavage of ring carbon–substituent oxygen bond), but the presence of such a unit is usually apparent from the increase in the  $m/z$  values by 14 daltons. Primary fragment ions undergo a series of subsequent eliminations to give secondary fragments, including losses of acetic acid ( $m/z$  60) or methanol ( $m/z$  32) by  $\beta$ -elimination, losses of acetic acid but not of methanol (Fig. 2) by  $\alpha$ -elimination, and losses via cyclic transition states of formaldehyde, methoxymethyl acetate, or acetoxymethyl

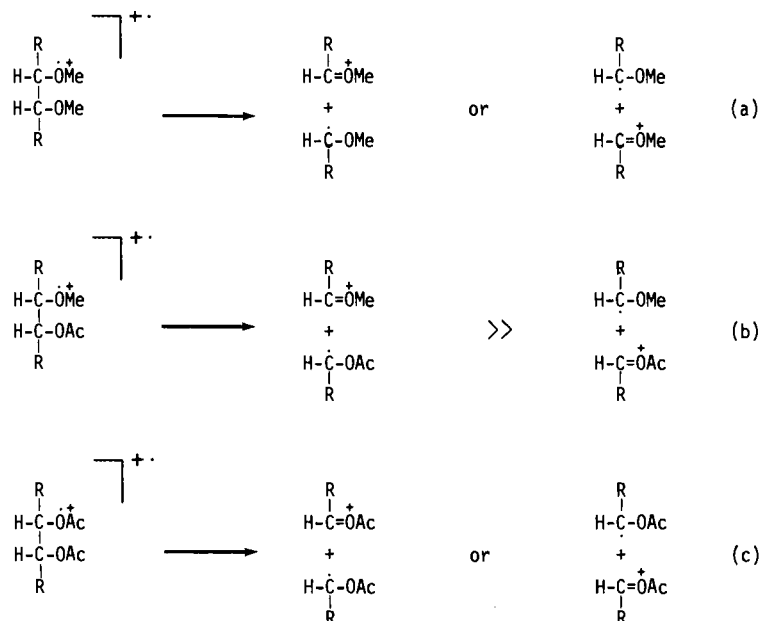


FIG. 2. Primary fragment ions arising by  $\alpha$ -cleavage in the mass spectra of partially methylated alditol acetates.

acetate. A very valuable collection of mass spectra together with retention time data has been published for partially methylated alditol acetates from methylated hexoses, pentoses, 6-deoxyhexoses, and some heptoses and dideoxyhexoses (76MI5). Mass spectra of these and a variety of other carbohydrate derivatives have been reviewed (74MI1) and some salient features are outlined in this report. More recently, an account has been published of GLC data and mass spectra of derivatives of aminohexoses and aminohexitols (80MI6).

The main limitation of the use of partially methylated alditol acetates for the characterization of methylated sugars lies in the structural symmetry that may exist when the primary hydroxyl group (O-5 in pentoses and O-6 in hexoses) is not etherified. This difficulty, however, can be overcome by introducing deuterium at C-1 by reduction of the sugar with sodium borodeuteride.

Partially methylated, acetylated aldononitriles are acyclic derivatives readily formed from reducing sugars by reaction with hydroxylamine in pyridine, followed by the addition of acetic anhydride to effect elimination of acetic acid from oxime acetates and acetylation of unsubstituted hydroxyl groups. These derivatives, although less extensively used, appear to give good GLC separations, and their mass spectra can be readily interpreted without the problem of structural symmetry (75MI3).

Partially ethylated alditol acetates may be used as alternative sugar derivatives when separation difficulties are encountered with particular combinations of the corresponding methylated compounds (74BMS263; 75MI4).

Permethylated oligosaccharide alditols are often the most convenient derivatives to prepare from reducing oligosaccharides isolated as partial hydrolysis products. As in the case of partially methylated alditol acetates, reduction is best performed with sodium borodeuteride in order to avoid ambiguities arising from otherwise structurally symmetric terminal units. Spectra may be analyzed by considering, in turn, fragment ions derived from reducing and nonreducing terminal units and then fragment ions arising from internal units, often by more complex fragmentation pathways.

A mass spectra nomenclature scheme for oligosaccharide derivatives was developed by Chizhov and Kochetkov (66MI1) and later modified by Kovacic *et al.* (68MI1; 68MI2). In this scheme for unbranched oligosaccharides, sugar residues are designated by lowercase letters starting from the nonreducing end group (a) along to the unit derived from the reducing terminus—in the example shown in Fig. 3, the alditol residue (c). In this example, fragment ions are generated by a variety of bond-cleavage processes, and the various pathways are denoted by uppercase letters (A, B, etc.). Additional numerical subscripts indicate successive ions along a given pathway. Some examples are shown below and incorporate the further conventions that the first lower case letter indicates the ring unit that has undergone cleavage and that subsequent lowercase letters denote unaltered residues that remain attached as substituents.

Methylated alditol units in oligosaccharides are cleaved in a manner similar to that described previously for partially methylated alditol acetates. On the other hand, substituted cyclic carbohydrates undergo a variety of types of fragmentation, the most important of which are summarized in Fig. 4 for simple permethylated glycosides.

The most easily recognizable fragment ions in the mass spectra of permethylated oligosaccharide alditols are those from nonreducing units, i.e., fragment ions at  $m/z$  219 for permethylated hexose,  $m/z$  189 for permethylated deoxyhexose,  $m/z$  175 for permethylated pentose,  $m/z$  233 for permethylated

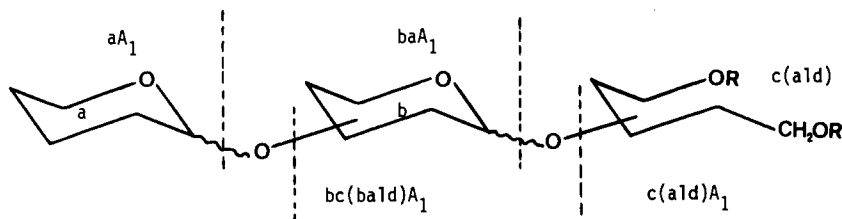


FIG. 3. Mass spectral nomenclature for fragment ions from oligosaccharide derivatives.

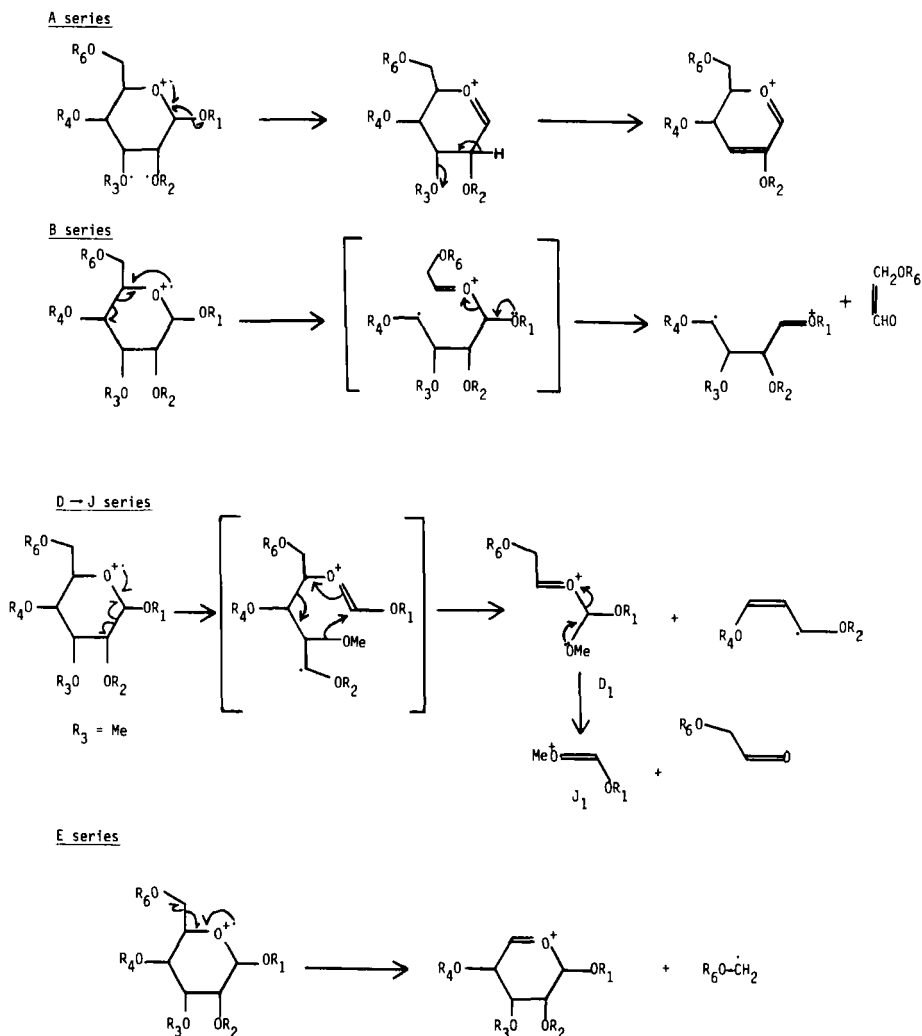


FIG. 4. Some typical mass spectral fragmentation pathways for permethylated glycopyranosides.

hexuronic ester, and  $m/z$  260 for permethylated *O*- and *N*-2-acetamido-2-deoxyhexose residues (see fragment  $aA_1$  on Fig. 3). Likewise, from 1-*d*-labeled alditol residues from reducing termini, the following ions are readily recognized;  $m/z$  236, 206, 192, and 277 for units derived from hexose, deoxyhexose, pentose, and 2-acetamido-2-deoxyhexose residues, respectively [see fragment C(al) on Fig. 3]. Furthermore, information on the general nature of unbranched internal units can be obtained by detecting, in the  $m/z$  values

for fragment ions of higher mass, increments of 204, 174, 160, 218, and 245, respectively, for hexose, 6-deoxyhexose, pentose, hexuronic ester, and 2-acet-amido-2-deoxyhexose units (see fragment  $\text{baA}_1$  on Fig. 3). These aspects of mass spectrometry, therefore, allow conclusions to be drawn concerning the sequences of sugar units when these are of different types only. On the whole, very little information, if any, can be obtained concerning stereochemistry, either of individual residues or of the configuration of glycosidic linkages. Nevertheless, some information can be obtained on linkage types from an examination of fragmentation pathways.

The use of primary fragment ions is not enough to allow for extensive structural characterization. Careful examination, however, of the secondary fragmentation pathways provides a more precise means to identify some, but not all, of the structural characteristics for the substance under study. Aspinall (82MI7) reviewed a useful example in which the permethylated alditols from the milk oligosaccharides lacto-*N*-tetraose [ $\text{Gal-}\beta(1 \rightarrow 3)\text{-Glc-}\beta(1 \rightarrow 3)\text{-Gal-}\beta(1 \rightarrow 4)\text{-Glc}$ ] and lacto-*N*-neotetraose [ $\text{Gal-}\beta(1 \rightarrow 4)\text{-Glc-}\beta(1 \rightarrow 3)\text{-Gal-}\beta(1 \rightarrow 4)\text{-Glc}$ ] (77JBC1014; 77JBC1023) are analyzed. The information that can be so obtained in some cases includes evidence for a 3-linked glycosyl substituent (presence of  $\text{A}_1$  and  $\text{A}_2$  ions, see Fig. 4), the differentiation between 2- and 4-linked residues in methylated di- and trisaccharides (73MI2), and the recognition of branched oligosaccharide alditols in which the alditol unit carried two glycosyl substituents (80MI8). Care should be taken, however, as the structures presented for the fragment ions are not exhaustive and several others are possible (82MI7).

## B. CHEMICAL IONIZATION AND DESORPTION CHEMICAL IONIZATION (80AC1589A)

Most investigations of the chemical ionization (CI) mass spectral behavior of saccharides have employed methane, isobutane, ammonia, helium ( $\text{e}^-$  capture), or a combination of these gases. The reacting forms of these gases are  $\text{CH}_5^+$ ,  $\text{C}_4\text{H}_9^+$ , and  $\text{NH}_4^+$ , which decrease in their protonating capability in the order shown. Thus, fragment ions are quite abundant in the methane and isobutane spectra of saccharides, whereas the ammonia CI spectra are dominated by ammonia cluster and sample adduct ions (72TL4827).

The first carbohydrate-ammonia CI study reported single adduct ions for peracetylated mono- and disaccharides and also indicated that for underivatized materials smaller fragments corresponding to the loss of water from the molecular ion adduct are observed (65JCP449). Since this early work, considerable carbohydrate mass spectral data, obtained by CI with ammonia as a reagent gas, have accumulated (71AC28A; 72TL4827; 73MI4; 74JOC451;

74MI2; 77MI4; 78MI9; 79AMS1660; 79BMS242; 79BMS415; 80BMS127; 81BMS265; 81BMS278; 82MI1 p 730). With few exceptions, however, little work has been published on fragment ion structures and because of the different methods of sample introduction, various reagent gas pressures and mixtures used, and the poor quality of mass spectra reproduced in many journals, it is difficult to judge and compare the contributions of these parameters to the resultant spectra or to draw definitive conclusions.

Specifically, one difficulty in reviewing CI mass spectral work is the separation of CI-induced fragmentation from that due to pyrolysis, a variable which is highly dependent upon the method of sample introduction. This factor is frequently overlooked, and fragmentation schemes have been proposed with all ions originating from the adduct or protonated molecular ion (74MI2; 82AC2456).

The first detailed look at carbohydrate oligomers using ammonia CI was reported in 1974. The investigators studied a series of peracetylated oligosaccharides introduced on a solid probe and chose to enhance fragmentation by the addition of isobutane at half the concentration of ammonia (74JOC451). The use of a multicomponent reagent gas further complicated the identification of the origin of the various fragments. Nevertheless, peracetylated saccharides produced a number of even-mass fragments indicating that they contained nitrogen. This observation led to the proposal of four possible ways in which this nitrogen may be incorporated (74JOC451):

1. Ammonium attachment to neutral fragments (i.e., thermalized intact molecules and pyrolysis products);
2. Adduct ion degradation via loss of a small molecule (e.g., HOAc, H<sub>2</sub>O);
3. Attachment of neutral ammonia to charged fragment ions (i.e., CI-induced fragments);
4. Covalent bond formation followed by ionization (e.g., formation of carbinolamines).

Experimental support for one of these mechanisms was obtained by metastable ion studies which followed the loss of acetic acid from the molecular ion adduct (74JOC451). Further fragmentation studies were pursued in later work using the same mixtures of isobutane and ammonia as the reagent gases, but with reduced and permethylated carbohydrate derivatives (76JOC3425). The samples analyzed included six disaccharides and two trisaccharides and the spectra provided sequence information and some indication of linkage based on fragment ion abundances. These studies clearly indicate that fragments do arise from the ammonium ion adduct. However, the use of a mixed reagent gas to enhance fragmentation, as already noted, obscures the influence that ammonia itself may contribute to the spectrum.

Several overall features of oligosaccharide's ammonia CI spectra are worthy of consideration.

1. The stability of the molecular ion adduct;
2. The enhanced ion abundance for rupture at each glycosidic linkage;
3. Also related to the glycosidic cleavage, the ions differing by 2 daltons which appear at the expected incremental intervals of 204 daltons, which corresponds to the incremental mass of a permethylated glycosidic unit. These ion pairs are of considerable importance for sequence interpretation and their origin appears clear. However, the exact structures of these ions have not been clarified.

Probably the most interesting glycoside work, from the standpoint of carbohydrate sequencing, has been that reported for the cardiac glycosides (79AMS1660; 80MI9). Using ammonia DCI, spectra were obtained for two trisaccharide-containing samples, dioscin and digoxin, which exhibited a series of ions for sequential loss of terminal pyran-oxonium sugar residues from the charged aglycone. No sequence ions starting from the terminal carbohydrate end could be detected. The spectra provided ample high-mass and molecular weight related ions in addition to the sequence information.

Several other glycoconjugates such as saponins (81HCA297), cardenolides (79BMS415; 80MI9), glucuronides (82AC2456), glucosinolates (81BMS265; 81BMS278), flavone glycosides (81HCA297), cyanogenic glycosides (82BMS307), and the aminoglycoside antibiotics (82OMS247) have been studied by CI-MS. Again, although molecular weight information was obtained easily, the amount of structural data so obtained was of almost no value.

### C. FIELD DESORPTION AND FIELD IONIZATION

Field desorption (FD) and field ionization (FI) mass spectrometry are today two of the best known soft ionization methods (77MI7; 77MI8). FD has been important since the early 1970s in biomedical, chemical, and environmental research for the analysis of compounds which are involatile, thermally labile, and of high molecular weight [for recent reviews, see (79MI3) and (82MSR63)]. Since FD generates ions related to the molecular weight even for salts and very polar organic materials, derivatization may be avoided. This has the advantage of eliminating the need to worry about the stability of the sample during chemical manipulations or whether the weight of the derivative is beyond the mass range of available instrumentation.



From its inception in 1969 (77MI7), FD has been applied to the structural characterization of carbohydrates and glycoconjugates (79MI3; 80MI3; 82MSR63). The FD spectra of free sugars and di- and trisaccharides (in the absence of alkali salts) are dominated by  $[M + H]^+$  and  $[M + H - H_2O]^+$  ions and exhibit little or no fragmentation at lower emitter currents (12–15 mA) (71OMS983; 74OMS903; 75AG(E)403). At higher heating currents (15–18 mA) sequence-informative ions are produced by cleavage on either side of the glycosidic oxygens. For example, the FD mass spectrum of raffinose recorded at 18–19 mA exhibits a base peak at  $m/z$  505, which corresponds to  $[M + H]^+$ , and abundant fragment ions at  $m/z$  163 and 343. At higher emitter current an additional ion at  $m/z$  325 is observed as well as many low-mass peaks due to fragmentation of component sugar residues.

The mechanism of fragment ion formation may be similar to the acid-catalyzed hydrolysis of carbohydrates in solution (78T1003). Cleavage on the terminal side of the glycosidic oxygen produces the terminal 1-deoxysaccharides, and some pyranoxonium species (ions at, e.g.,  $m/z$  163, 325, ..., etc., for aldohexoses—see A series in Fig. 5). Alternatively, cleavage on the reducing end of the glycosidic oxygen with hydrogen and proton transfer results in the protonated terminal saccharide ion (such as at  $m/z$  343) in the spectrum of maltotriose (74OMS903). No correlation between stereochemical considerations and the occurrence of one or the other fragmentation has been made. These fragments could also arise through hydrolytic interaction of bound water with the sugars on the emitter surface (77OMS28). Charge retention on the reducing end of the molecule would result in a series of fragments that are isobaric with those from the terminal end. Thus, to define more precisely the origin of these fragments, the FD spectra of oligosaccharides could be compared before and after reduction with  $NaBH_4$ . These results indicate that the charge is localized preferentially on the terminal (nonreducing) end of the oligomer for saccharides with fewer than five residues, but with increased chain length there is a gradual shift to charge retention on the reducing end (83MSR153).

Early FD studies of saccharides suggested that molecular weight information might be difficult to obtain for oligomers containing more than three residues (74OMS903). More recently, however, spectra for larger oligosaccharides have been reported for samples in which alkali metal ions are present or have been added (76AG(E)696; 77OMS28; 77OMS710; 77T2825).

The success of model studies (77OMS28; 82AC299) has prompted the application of FDMS to high-molecular-weight oligosaccharides of biological significance. Structurally informative fragments were observed in the FD mass spectra of  $(Man)_8-Glc-NAcH_2$  [eight mannose units linked to an *N*-acetyl glucosamine alditol (81PNA1471)], which has a calculated molecular weight of 1520.53. In this example, loss of the terminal mannose residue by

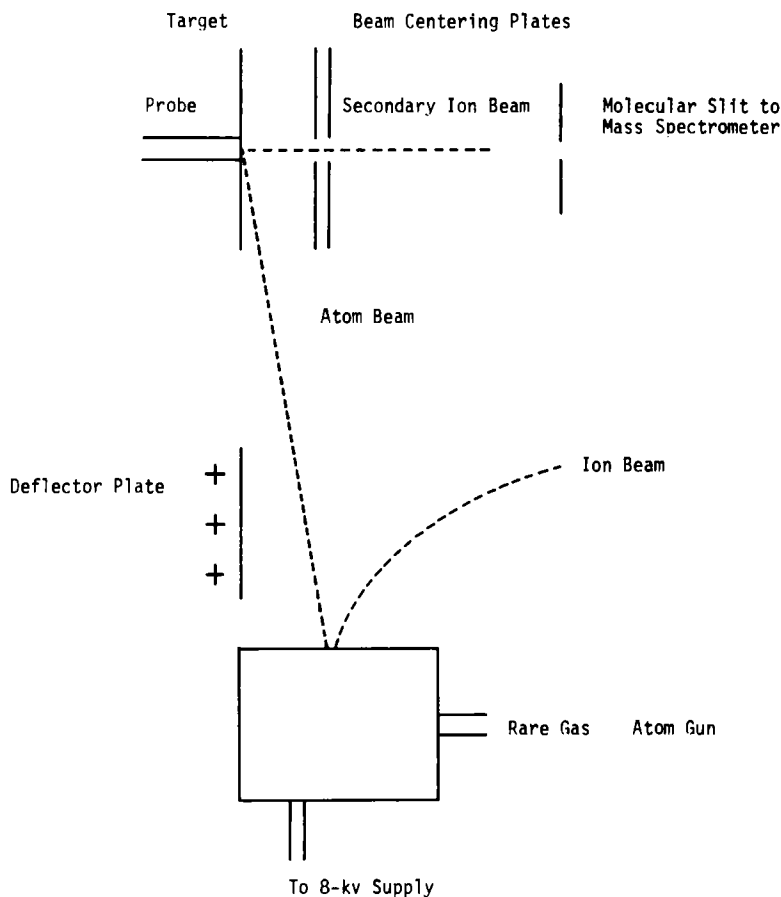


FIG. 5. Overall diagram of a fast atom bombardment ion source.

cleavage on the nonreducing side of the glycosidic oxygen is accompanied by proton transfer resulting in ions corresponding to  $[M - 162 + Na]^+$  and  $[M - 162 + H]^+$ , with calculated masses of 1381.47 and 1359.49 daltons, respectively. Loss of the terminal disaccharide fragment is also indicated by the ion at  $m/z$  1219 =  $[M - 324 + Na]^+$ . However, care must be taken because contamination by shorter oligomers would result in the same series of ions.

Recent developments in magnet technology have provided mass spectrometers that can transmit ions heavier than 3000 daltons at full accelerating potential and high sensitivity. Instrumentation with such extended performance capability was used to obtain FD mass spectra of a mixture of the higher molecular weight methylmannose oligosaccharides (81BMS463).

Abundant ions were observed at  $m/z$  2154, 2330, and 2506, which correspond to the  $[M + Na]^+$  ions of  $Man(MeMan)_xOCH_3$ , where  $x = 11-13$ .

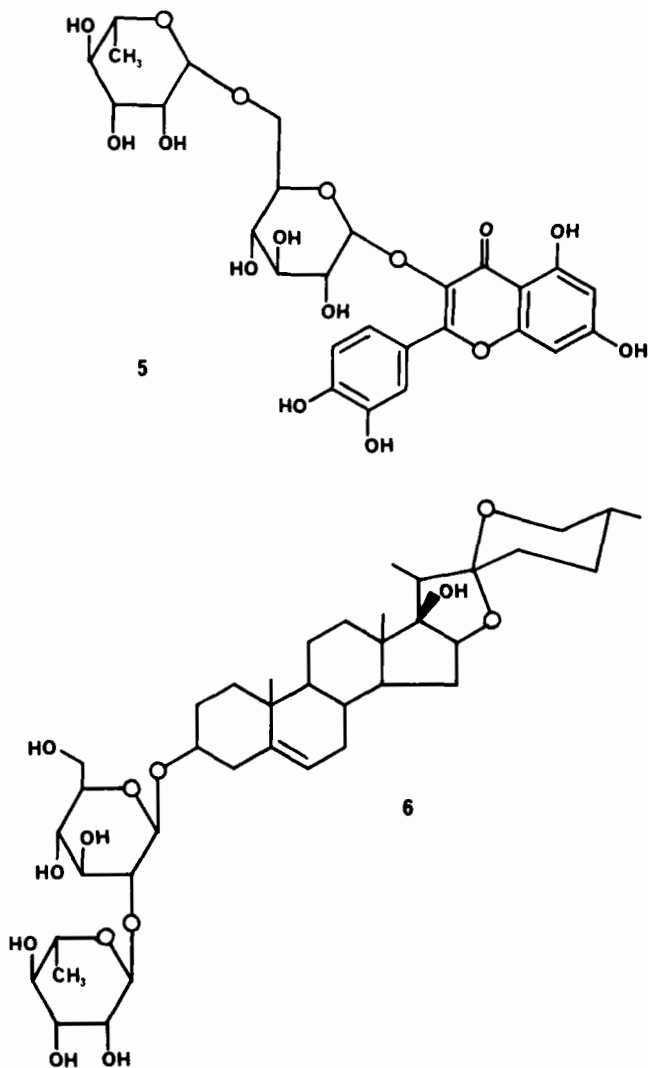
Undoubtedly, the excellent results obtained for this series of compounds are due, in part, to the increased volatility and stability imparted by the presence of methyl groups on approximately one-third of the available hydroxyl groups. This suggests that FDMS of synthetically permethylated oligosaccharides may allow the molecular weight characterization of even larger polymers. Preliminary work on fully permethylated di- and trisaccharides indicated that the relatively high volatility of these compounds results in poorly reproducible FD mass spectra (74OMS903). Recently, however, FDMS has been successfully employed in the analysis of a 6-*O*-methylglucose polysaccharide isolated from *M. smegmatis* (82JBC3555) that contains 20 hexose units. Usable FD mass spectra could not be obtained on the native 6-*O*-methylated material, whereas the synthetic, fully permethylated eicosasaccharide gave clusters of peaks separated by 14 daltons (due to undermethylation or demethylation during desorption) up to approximately  $m/z$  4250 (calculated MW = 4230,  $[M + Na]^+ = 4253$ ), thereby confirming the degree of polymerization of the oligosaccharide. Masses were assigned by reference to a crystal time marker that had been calibrated under EI conditions with Fomblin oil. It should be noted that the underivatized 6-*O*-methylglucose polymer was readily analyzed by fast-atom bombardment mass spectrometry.

Peracetylated oligosaccharides have also been studied and these derivatives exhibit abundant  $[M - 60]^+$  ions and sequence informative fragments (74OMS903). However, peracetylation nearly doubles the weight of the sugar and, therefore, may be of limited practical value for large oligosaccharides.

During the late 1960s and early 1970s, a number of reports appeared which described the successful application of FI (77MI7) to the analysis of aromatic (71MI2) and steroidal glycosides (67ZN(B)121; 71OMS573). This work [described in detail in a recent review (80MI3)] clearly demonstrated that FI could provide the weights and sequence of the component monosaccharides and the molecular weight of the intact molecule and aglycone for underivatized glycosides containing up to three sugar residues.

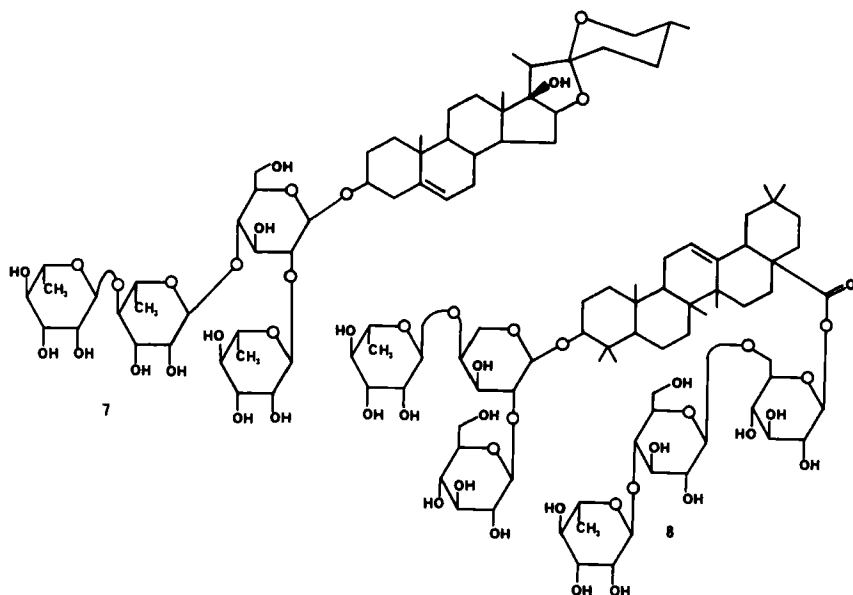
These early successes suggested that FD would be a promising analytical approach for less volatile glycosides containing even longer carbohydrate moieties. A series of underivatized *O*-glycosides of varying sugar compositions and genin structures were subsequently studied by FDMS. These results gave comparable information to that obtained by FIMS, but the FD spectra were more intense and showed less fragmentation.

Examples of successful experiments include complex molecules such as rutin (**5**) (83MSR153), saponins such as pennogenin-3-*O*- $\beta$ -L-rhamno-pyranosyl- $\beta$ (1  $\rightarrow$  2)-glucopyranoside (**6**) and its tetrasaccharide counter-



part 7 (77T2595; 78T1003; 79LA811; 79ZN(C)1094), and higher molecular weight pentacyclic triterpene saponins such as that presented as structure 8 (78T1003).

Some attempts have been made to correlate the known rates of hydrolysis of various sugars in aqueous acidic media with the observed relative abundances of ions in the FD mass spectra (77OMS2595; 78T1003; 79LA811; 79ZN(C)1094; 81LA683). For example, it is known that D-xylosides hydrolyze about five times as fast as D-glucosides in solution. Similarly, the ratio for loss



of terminal xylose to terminal glucose in the FD mass spectrum of the glycoside tomatine was found to be 2.8:1 (79ZN(C)1094). However, there are many exceptions to the analogy and, therefore, more model systems must be studied before conclusions can be made for glycosides of unknown structure.

From these results it is apparent that FDMS is highly successful in obtaining both molecular weight and sequence information for complex carbohydrates and glycoconjugates. Undoubtedly, FDMS will continue to be relied on as a physical method for the structural analysis of these molecules.

#### D. LASER, PLASMA, AND FLASH DESORPTION

Laser desorption (LD) mass spectrometry, like secondary ion mass spectrometry (SIMS), was developed primarily as an analytical tool to study inorganic elements on surfaces (80MI10; 82AC26A). However, shortly after the introduction of this technique, salts of simple organic molecules were shown to yield abundant cationized molecular ions by LD (68AMS107). Since that time, LD has been shown to have remarkable potential for obtaining molecular and structural information on complex involatile biomolecules (75MI4; 78AC985; 80AMS928). These observations, combined with the recent availability of commercial instrumentation, have sparked a resurgence of interest in LD (78MI4; 80AMS942; 80OMS295; 81AC1492).

Under LD conditions, alkali metal cation attachment is the dominant ionization process. Protonated molecular and fragment ions are generally not

observed for carbohydrates under these conditions (78AC985). In addition to the abundant pseudomolecular ion  $[M + \text{alkali}]^+$ , fragment ions corresponding to alkali-cationized saccharides (mono-, di-, tri-, etc.), pyranoxonium saccharides (mono-, di-, tri-, etc.), and ring ruptures are observed. No stereochemically related influence on the spectra has been reported.

As observed in other ionization techniques, addition of salts shifts both molecular and sequence-informative fragments by the mass difference of the added cation. Salt addition to carbohydrate samples is usually unnecessary for obtaining good LD mass spectra because sufficient quantities are often present in the sample or on the support surface (78AC985). However,  $\text{Na}^+$  doping of ethanol solutions of carbohydrates has been reported to improve the sensitivity for their analysis under LD conditions (80AMS942; 82AC280A). Other matrix effects may also have a significant contribution to LD mass spectra, but experience with biomolecules is still very limited. Few glycoconjugates have as yet been analyzed by LD, but preliminary data for some steroidal glycosides demonstrate that excellent results can be obtained using this technique (78AC985).

A relatively new method that shows promise for the analysis of biomolecules is that of plasma desorption (PD) (e.g., from californium-252) (74BBR 616; 76MI6; 76MI7; 82AC43A; 82AC105A). Commercial instrumentation has been available only recently and too few applications to carbohydrate structural problems have appeared to allow for a good appraisal of the technique and to warrant any greater coverage of the technique.

Another method, not technically related, that shows promise and that has been used more extensively than PD in analysis of oligosaccharides, although still not enough to be fully evaluated, is that of flash desorption (78JA1974; 79ACR359; 82SIJ110). In these papers, Daves and co-workers have clearly shown that this technique has some value. It appears unlikely, however, that it will develop into a standard analytical method.

## E. SIMS AND FAB

The SIMS and fast-atom bombardment (FAB) mass spectra of oligosaccharides are remarkably similar in appearance to each other and to the corresponding FD spectra. Under SIMS conditions, ions are formed from the sample, from the metal substrate, and from ion/molecule reactions occurring between the two (80AC557A). Take, for example, the SIMS spectrum of stachyose deposited on a silver target.  $\text{Ag}^+$ ,  $[\text{fragment} + \text{Ag}]^+$ , and  $[M + \text{Ag}]^+$  ions are recorded (81AC2340; 81OMS167). Because silver has two nearly equally abundant stable isotopes (107 at 51.83% and 109 at 48.17%) the argentated ions form readily recognizable doublets. Ions arising from the sample support are not usually evident in FAB mass spectra unless

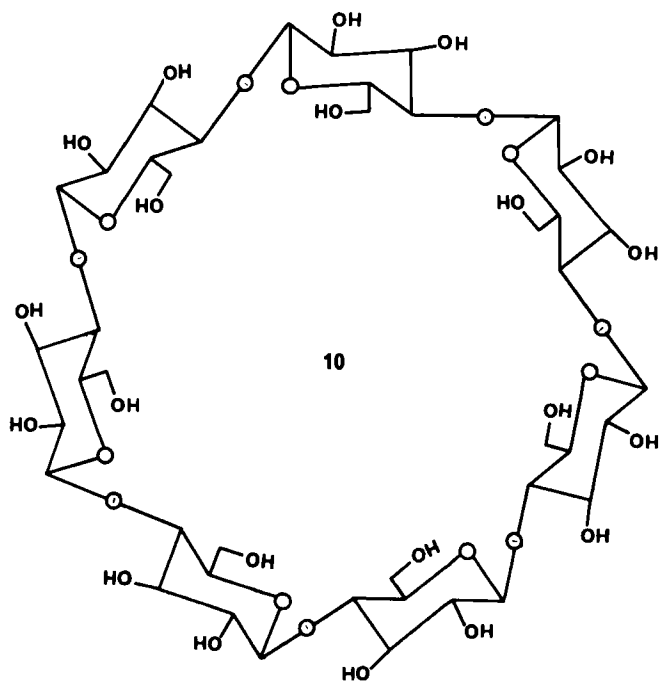
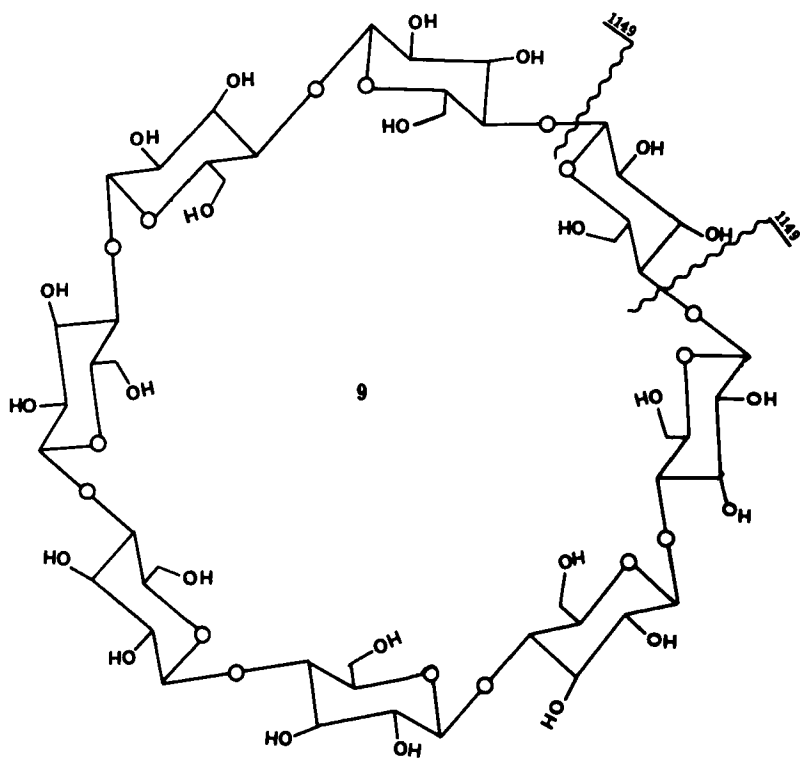
a portion of the target becomes directly exposed to the primary beam as a result of glycerol depletion.

Cationization also occurs with alkali metal ions present in the sample or as impurities on the substrate surface. In SIMS such ions are usually very abundant, whereas in FAB,  $[M + H]^+$  and  $[\text{fragment} + H]^+$  ions may dominate because glycerol is a good source of protons. As observed in FD, doping with salts increases the contribution of cation-containing species in both the FAB and SIMS spectra. However, preliminary evidence indicates that high concentrations of alkali cations decrease the relative abundance of fragment ions in the FAB spectra of many compounds, including carbohydrates, and therefore should be avoided (82MI1p728, p 730).

The nature of the sample matrix also has a marked effect in FAB. For example, glycerol gives rise to a characteristic spectrum of its own which consists chiefly of cationized polymers of the type  $[(\text{glycerol})_x + H]^+$  (82AC645A). In addition, ions are observed at every nominal mass, which presumably arise from fragmentation of glycerol and its polymers at or near the points of primary beam impact. Carbohydrates, like glycerol, exhibit peaks of lower relative intensity 2 daltons below fragment, molecular, and adduct ions. These ions are also present in the SIMS mass spectra of carbohydrates (81AC109), and may arise from oxidation occurring in the gaseous high-pressure region directly above the probe surface. An earlier report has suggested that improved results can be obtained for oligosaccharides when 3-mercapto-1,2-propanediol (thioglycerol, MW = 108) is used as the liquid matrix (83MSR153) because the contribution of matrix-related ions at higher masses is substantially lower and the intensity of sample-related ions is often greater (two- to fivefold) than observed with glycerol. A hidden trap not recognized by these authors will be discussed in Section IV. Furthermore, the greater volatility of thioglycerol reduces the effective observation time to minutes, although cooling of the sample may obviate this problem.

A review of empirical results to late 1982 is available (83MSR153). Unfortunately, however, it does not present the data in a way that leads to any interpretative conclusions. The coverage of SIMS and FAB in this section is limited and is discussed in greater detail under Section IV.

Although complex oligosaccharides of biological origin have only just begun to be examined by FAB and SIMS, preliminary data suggest that these techniques will have a major impact on carbohydrate mass spectrometry. A partial negative ion FAB mass spectrum of  $\gamma$ -cyclodextrin (cyclo-octylamylose) (9) shows a prominent  $[M - H]^-$  along with a fragment ion at  $m/z$  1149 due to excision of a dideoxyglycoside unit (81M14). The positive ion FAB mass spectrum of  $\beta$ -cyclodextrin (cycloheptylamylose) (10) is surprisingly rich in structural detail (82M11). Abundant sequence ions of the





type  $[(O\text{-hexose})_n + H]^+$  (where  $n = 1-6$ ) are present; the smaller members of this homologous ion series carry a larger percentage of the ion current. The molecular region of the spectrum shows a prominent  $[M + H]^+$  as well as  $[M + H + \text{glycerol}]^+$  and  $[M + H + (\text{glycerol})_2]^+$  ions.

Other preliminary data indicate that FAB could be useful in obtaining the molecular weights of complex oligosaccharides such as the oligomannosides found in the urine of patients suffering from glycoproteinoses or glycolipidoses (79MI4). In preliminary work the FAB mass spectrum of the branched deca-saccharide (Man)<sub>9</sub>-Glc-NAc exhibited  $[M + Na]^+$ ,  $[M + H]^+$ , and  $[M + H - H_2O]^+$  peaks (at  $m/z$  1702, 1680, and 1662, respectively) with good signal-to-noise ratios after 0.1 M HCl had been added to the sample in glycerol. Unfortunately, sequence-informative fragments were of negligible abundance. Both FAB and SIMS have also shown considerable promise for the analysis of glycosides (82MI2; 82MI3; 82SIJ132).

### III. A Closer Look at FAB-MS

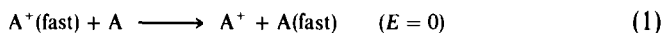
Fast-atom bombardment mass spectrometry (FAB-MS) is a renewed old technique although it is most often thought of in terms of a novel mass spectral technique. As early as 1966, Devienne and co-workers (66CR(262)696) presented data on a technique that they called molecular beam for solid analysis (MBSA). The idea was further developed by the same group (67MI1; 68MI3; 73MI6; 73CR(276)923; 74CR(B)(278)165; 74CR(C)(278)1219; 76CR(B)(283)397) but was largely ignored until the announcement by Barber *et al.* (81CC325) and by Surman and Vickerman (81CC324) of the re-discovery of FAB. A number of symposia and workshops devoted in whole or in part to the understanding of FAB and its applications followed (81MI5; 81MI6; 82MI1; 83MI1; 84MI1; 85MI1; 86MI1). Despite all of these efforts and an update by Devienne and Roustan (82OMS173), no definitive reports dealing with FAB fundamentals have been presented to date, although the literature describing its applications has seen an explosive growth.

#### A. PRINCIPLES AND INSTRUMENTATION

The overall diagram of a fast-atom bombardment ion source is depicted in Fig. 5. This is fairly simple, consisting of three main elements: (1) an atom gun, (2) a sample inlet, and (3) an ion-extraction system.

The atom gun is made up of an evacuated chamber that encloses a plate to which a high voltage potential (nominally 8 kV) is applied. The gas to be used as the bombardment gas is allowed in the chamber, through an appropriate

inlet, where it is ionized by the high potential plate. The ion beam so created is repelled by the same plate (at 8 kV) and, to a certain extent, regains its neutral character by electron-capture or by charge-resonance. Since the atoms do not suffer much loss in momentum they exit the atom gun and are aimed at the target where the sample is located. A high voltage plate, positioned at an angle of  $90^\circ$  relative to the atom beam, is used to deflect all of the remaining ions that have not been neutralized by charge-resonance. Thus, only the atom beam will reach the sample to be analyzed. In the past, workers in the field have used separate charge-exchange chambers (34MI1) to carry out the neutralization process described above. However, the source becomes extremely simple once it is realized that any high-pressure confined-discharge ion source will produce large quantities of fast neutral species. These arise by charge-resonance exchange between the ions produced in the discharge and the high-pressure nonionized gas in the gun itself [Eq. (1)].



Saddle field ion sources such as those by Ion Tech Ltd. (74MI3) are very compact, simple, and efficient; they have been widely adopted for this purpose. Their characteristics are well documented and they have been used by Barber *et al.* during the course of their development of FAB (81MI7; 82AC645 A).

A typical sample inlet is shown schematically in Fig. 6. The sample is loaded onto the tip of a probe along with a support matrix which is inserted into the

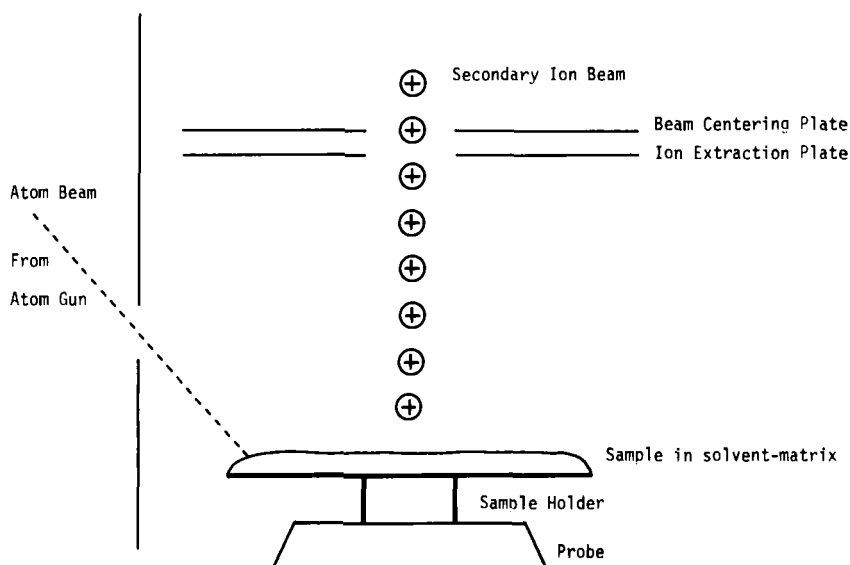


FIG. 6. Schematic diagram of a FAB ion source.

conventional ion source of the mass spectrometer at a location such that it intercepts the incoming beam of fast neutrals (from the atom gun). The angle of incidence of the beam is of importance, and an angle of  $70^\circ$  (i.e.,  $20^\circ$  with respect to the sample) is considered a good value (82AC645A; 82MI4). This gives rise to a sputtering phenomenon (Fig. 7) and the secondary ions so produced are then extracted into the mass spectrometer by an extraction plate (nominally at 3 kV) and a centering plate to focus the accelerated secondary ion beam into the molecular slit of the mass analyzer.

The technique is very closely related to another condensed-state ionization method, secondary ion mass spectrometry (78AC1180; 80AC557A), but differs from this in that the accelerated inert gas ions used in SIMS (81MI5p357; 82PAC267) undergo a charge-exchange process prior to bombardment of the sample. On a theoretical basis it can be argued that the bombarding ions in SIMS effectively become bombarding atoms through the Auger effect (81MI5p794). Experimentally, the same ion gun is used in both methods and it has been demonstrated that the ion beam in SIMS contains many neutral

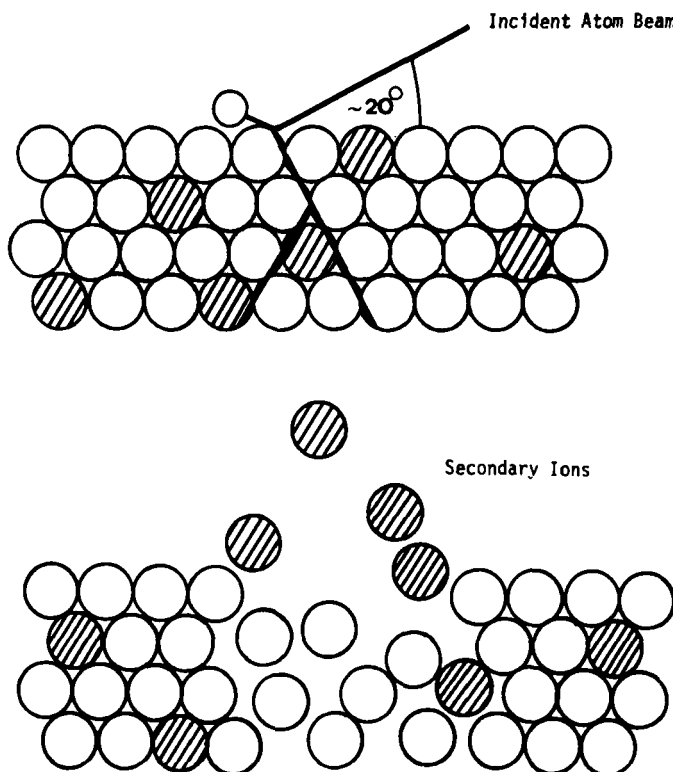


FIG. 7. Schematic of the sputtering phenomenon occurring in a FAB source.

atoms (82MI5), no means being deployed to prevent the spontaneous charge-exchange reactions from taking place. On the other hand, turning off the deflector plates (Fig. 5), used in FAB to clean the atom beam from residual ions that have not charge-exchanged, still produces a FAB-like spectrum. Devienne and Roustan, who have performed SIMS versus FAB studies on organics (see above), did not report on the evidence or lack thereof of a close similarity between the techniques and more recent SIMS studies indicate that it is possible to obtain SIMS results that are similar to those obtained by FAB (81AC2340; 82AC2029).

It is not expected that the types of analyzer and detector used in the mass spectrometer should be critical for the successful recording of FAB spectrum and, thus far, the literature supports this statement. Quadrupoles (81AC1704; 81CC324), single- and double-focusing magnetic instruments, as well as triple analyzers have been used (82MI1p323). By analogy to their use in SIMS experiments (81AC1241), time-of-flight instruments easily convert to FAB. New ion sources can be purchased for older instruments, or a saddle field ion gun can be attached with relative ease and little modification and expense to existing FD, EI, or CI sources (82MI1p564; 83OMS176). The most valuable aspect of FAB is its simplicity.

All other standard options of a modern mass spectrometer can also be carried out while using FAB as the ionization mode. Metastable studies and linked-scan techniques (82SIJ169) to assign ion fragmentation pathways are possible (81MI7; 83MI2; 83MI3), as are collisional activation experiments to enhance fragmentation (83BMS426; 83MI2; 83MI4). [Mass spectra obtained by FAB (including relative intensities) are reproducible when recorded on a given instrument as well as when recorded on widely different instruments (82MI1p390)]. High-resolution accurate mass measurements of FAB-generated ions were also shown to be possible (83MI5; 83MI6) but with some difficulty.

## B. SPUTTERING PHENOMENA

The sputtering phenomenon always held out the promise of being used as a general solid-state ionization technique. It has been used for some time as a means of surface and bulk elemental analysis of solids in the ion microprobe (62CR(255)1893). The phenomenon was first reported in 1852 (68MI4): if a solid is bombarded by high-velocity particles (e.g., rare gas ions of about 8-keV energy), then some of the solid material will be removed into the gas phase. This is the result of momentum transfer from impinging particles to the target, setting up collision chains (81MI8) as shown in Fig. 7. The sputtered material can bear either positive or negative charge. Robb and Lehrle (68AMS447) first

demonstrated the feasibility of such an ion source. However, credit is to be given to Benninghoven *et al.* (76MI8) along with MacFarlane (76MI6) for sharing the uniquely advantageous mass spectral results that can be obtained with organic compounds with such a source. The quality of the results obtained in these studies was limited by the inherent performance of the mass spectrometers that were used. The technology of producing fast beams of rare gas atoms with controllable kinetic energy is well known (67MI2).

### C. MATRIX SUPPORT

In early experiments charged particles sputter sources were used, and the sample was deposited as a solution onto the probe and the solvent was evaporated to dryness before analysis (76MI9). This method yielded mass spectra that were transient in nature with a relatively short lifetime (tens of seconds). Subsequently, it was noted, however, that low-vapor-pressure liquids and oils gave spectra that lasted for hours. Examples included a variety of pumping fluids such as Apiezon oils, Santovac 5, Convolex 10, and also some siloxanes frequently encountered as contaminants in organic samples. These early observations led to the search for low-vapor-pressure viscous solvents to make a solution of the material under study, thus mimicking the fluid behavior with solids (81CC325). One of the first successful solvents used was glycerol (81BJ401); it gave enhanced sensitivity (compared with solid sample preparations) and much longer sample lifetime (hours), provided that enough sample and glycerol were present to continue maintaining the fluid-like conditions.

A series of different solvents has also been used in FAB analysis: polyethylene glycol (PEG-200, -400, etc.), thioglycerol, ethanolamine, diethanolamine, macrocyclic ether (e.g., 18-crown-6), etc. Glycerol, however, is still, and by far, the most widely used solvent. These solvents exhibit their own characteristic spectra on top of that of the substance under study. This effect is often seen as a drawback as it can mask some of the peaks related to the solid sample and in most cases it complicates interpretation by adding unwanted peaks to the spectrum. For example, glycerol shows peaks of decreasing intensity at every  $(n \times 92) + 1$  daltons, corresponding to glycerol molecules solvating a proton. If a trace of a sodium salt is present, as is often the case with samples obtained from some form of chromatographic separation technique, then another series of peaks at every  $(n \times 92) + 23$  daltons arises in the spectrum. On the other hand, the molecules under investigation might have the right surfactant properties and bulk solubility to give a mass spectrum in which the solvent background is totally suppressed (81BJ401; 81MI9; 82AC645A).

It has been claimed, after studying chlorophyll *a*, that for best results, the solid sample needed to be dissolved in the solvent rather than simply dispersed (82AC645A). We have demonstrated that this was not prerequisite to successful recording of FAB spectra (85MI2; 86MI2). In principle, however, the objective is to submit the sample to the atom beam at a highly mobile surface concentration, and for maximum sensitivity the sample should form a perfect monolayer at the surface of a substrate having low volatility. This is a characteristic of compounds that exhibit high surface activity in aqueous media, attributable to the presence of highly polar or ionic groups, giving hydrophilic properties to an otherwise hydrophobic molecule. Monolayer formation at the surface of a dilute solution implies a constant surface excess concentration. Following Gibbs, this arises when the surface tension depends linearly on the logarithmic bulk concentration ( $\log_e C$ ) of the solution (81JPC25). The ratio of peaks due to glycerol to those due to the sample cation falls to zero as the monolayer becomes established. Under monolayer conditions, glycerol ions are absent from spectrum, and the solute exhibits a maximum sputter ion yield that is independent of the bulk concentration. Additionally, since there is no increase in ion yield as we increase the solution concentration in this range, we observe an "apparent" decrease in sensitivity measured relative to this concentration.

Since a monolayer of material is completely sputtered in a matter of seconds in a typical FAB ion source, it is essential that the sample surface be continuously regenerated during prolonged examination. This is done "naturally" by diffusion of the sample to the surface of the solution. It is therefore essential that the sample have some solubility in the low-volatility solvent, to provide the diffusion mechanism and also to act as a reservoir of material. Ionic groups that render compounds involatile, thus ruling out conventional methods of ionization, are also those groups that frequently lead to solubility in polar solvents, and to the associated surfactant properties that facilitate good sample preparation for FAB ionization. It follows that the detection of solvent substrate peaks in a FAB mass spectrum implies that optimal sample preparation has not been achieved.

The sputtering of neutral species, which are not detected by the mass spectrometer, is probably the major process occurring at the surface. Similarly, the simple sputtering of ions that are naturally present in the sample, undoubtedly, must constitute an important source of ions in FAB mass spectra. Consequently, sample preparation methods such as spiking with various additives which lead to an increase in the concentration of ionic material in the sample, can lead to an enhanced sensitivity (81AC25). Despite considerable speculation on the subject, the mechanism of ionization in the sputtering of nonionic compounds is uncertain. A recent review paper states that: "Good FAB mass spectra may be obtained with ease from compounds

that do not contain ionizable groups. Completely nonionic compounds, such as aliphatic hydrocarbons, do give good FAB mass spectra when the sample is in a condensed phase" (82AC645A). This statement contradicts previous reports to the effect that preionization is an essential factor for the obtainment of good FAB spectra (81JA5700), but complies well with the idea expressed above.

The complex solution and surface chemistry involved in a typical sample can lead to large apparent differential sensitivities between quite similar compounds (81BBR623; 81BBR632). Nevertheless, the FAB ion source has proved to be a valuable method for recording mass spectra of compounds that were previously considered to be intractable by MS because they were too ionic (81CC325) and too involatile. Without doubt, the californium-252 source is the leader in terms of bombardment technique with respect to high-molecular-weight determination, and this situation is likely to persist if we take into account the large amounts of energy available in this sputter process.

The exact role of the support matrix is ill-defined. In addition to the phenomenon just described, the matrix can influence stereochemical aspects by inducing, or forming, a given conformation of the sample and with such a high energy, it is also reasonable to assume that several solvent-solute reactions take place (84OMS101; 84UP1; 87UP1). It appears, therefore, that data on factors such as solubility, ionic character, charge localization, stereochemistry, degree of interaction between solvent and solute, volatility, and concentration are all necessary for the accurate prediction of the success, or otherwise, of an attempted FAB mass spectrum. The complexity of the process warrants some careful examination of the stereochemical aspects, however, since some of the factors previously mentioned (solubility, ionic character, etc.) are readily accessible and do not seem to be of prime importance in the cases presented to date (81JA5700; 82AC645A; 85AC1470).

## **IV. Recent FAB-MS Work on Carbohydrates**

### **A. SCOPE OF THIS SECTION**

The work described herein deals mainly with recent experiments aimed at evaluating FAB as a stereochemical probe. As it is shown in Section II, no definitive methods or rules are available in mass spectrometry for such analysis, although several reports indicate that it should be possible to make such use of this physical method. This is due to the relatively small amount of data available on FAB. Consequently, we will present several original data that we obtained in our laboratories and that are unpublished as yet.

In order to follow a systematic approach for these investigations, it is necessary to concentrate our efforts on one family of molecules. Our choice is

centered on oligosaccharides<sup>2</sup>, with the intention of probing the glycosidic bond. In order to achieve this goal the following experimental design can be followed.

1. Analysis of the FAB spectra of a series of oligosaccharides to determine whether or not some stereochemically dependent characteristics are exhibited.

2. In order to ensure that logical conclusions can be drawn, efforts will be concentrated on model compounds at first. Ideally, the latter should not have too high a molecular weight so as to allow for ready interpretation of the spectra where the features will be clearly related to the appropriate phenomena. Pairs ( $\alpha$  and  $\beta$ ) of disaccharides and glycoside monosaccharides meet that criterion, as they possess only one anomeric carbon, and they are readily available and well characterized. They also offer the possibility of looking at other stereochemical considerations at once (e.g., stereochemistry at C-4 for glycopyranoses) and allow for a direct evaluation of the effect of the substituent at the glycosidic bond (aglycone versus carbohydrate moiety) on the spectral characteristics.

3. Interpretative discussion will focus exclusively on positive ion data recorded in a glycerol support matrix. Some compounds will also be analyzed in other support matrices (with or without doping) to allow for a preliminary insight into the solvent, matrix, and charge effects.

4. Variations in the data will be discussed in terms of the stereochemistry of the glycosides used and correlated to existing stereoelectronic concepts. This leads to a discussion on the effects glycerol has on the type of compounds studied (and on those being used as a dispersive/dissolution medium).

5. Analysis of some higher oligosaccharides, derivatives, and saponins are included so as to provide for other insights into the universality, or not, of the phenomena encountered during the disaccharide/glycoside monosaccharide analysis, and on the eventual use of the technique in oligo- and polysaccharide sequencing. This is a preliminary stage, however, and the evaluation of the sequencing possibilities of the technique will be second to the establishment of rules for FAB analysis with respect to stereochemistry.

## B. EXPERIMENTAL

Original data reported (87UP2) here were recorded with commercially obtained reagents, solvents, carbohydrates, gases, etc., with the exception of (1) 1-*O*- $\beta$ -D-mannopyranosyl-L-erythritol, (2) 3-*O*- $\beta$ -D-galactopyranosyl-D-arabinopyranoside, (3) 1-*O*-phenyl-4-*O*- $\beta$ -D-galactopyranosyl-D-glucopyranoside, (4) *O*- $\alpha$ -D-glucopyranosyl-(1  $\rightarrow$  3)-*O*- $\beta$ -D-fructofuranosyl-(2  $\rightarrow$  1)-

<sup>2</sup> Other oxygenated heterocycles follow (Section V).



$\alpha$ -D-glucopyranoside (melezitose), (5) *O*- $\beta$ -D-glucopyranosyl-(1  $\rightarrow$  3)-*O*- $\beta$ -D-glucopyranosyl-(1  $\rightarrow$  4)-D-glucopyranoside, (6) 4-*O*- $\beta$ -D-glucopyranosyl-D-glucopyranoside octaacetate (cellobiose octaacetate), and (7) 4-*O*- $\alpha$ -D-glucopyranosyl-D-glucopyranoside octaacetate (maltose octaacetate), which were gifts from Prof. A. S. Perlin (McGill University), and of psoluthurin A (81TH1; 83CJC1465) and frondoside A (84TH1; 87UP3), which have been isolated from marine sources in our laboratories.

Original FAB spectra were recorded at room temperature using xenon as neutral atom source on a VG-7070E equipped with a FAB source and a VG data system, whereas linked-scan experiments were recorded on a Finnigan MAT-312 mounted with a saddlefield fast atom gun and controlled by a Finnigan INCOS data system (scan range 100–1300, scan time 10 sec). Both instruments were using an Ion Tech Ltd. power source and were operating at 8 kV (atom gun) and at a xenon pressure of  $1.5 \times 10^{-5}$  mbar at full accelerating voltage. Linked-scan spectra were recorded from the spontaneous unimolecular decomposition processes and in no cases were they collision induced.

### C. NOMENCLATURE

Throughout this section use will be made of the common names given to the various oligosaccharides under study so as to limit space and for a greater ease of reading. A list of proper names follows, however, along with the respective common name in parentheses, in order to establish the nomenclature and to avoid any confusion.

#### 1. *Monosaccharide Glycosides*

1-*O*-*p*-nitrophenyl- $\alpha$ -D-galactopyranoside ( $\alpha$ -*p*-nitrophenylgalactose); 1-*O*-*p*-nitrophenyl- $\beta$ -D-galactopyranoside ( $\beta$ -*p*-nitrophenylgalactose); 1-*O*-methyl- $\alpha$ -D-glucopyranoside ( $\alpha$ -methylglucose); 1-*O*-methyl- $\beta$ -D-glucopyranoside ( $\beta$ -methylglucose); 1-*O*-*p*-nitrophenyl- $\alpha$ -D-glucopyranoside ( $\alpha$ -*p*-nitrophenylglucose); 1-*O*-*p*-nitrophenyl- $\beta$ -D-glucopyranoside ( $\beta$ -*p*-nitrophenylglucose); 1-*O*-phenyl- $\alpha$ -D-glucopyranoside ( $\alpha$ -phenylglucose); 1-*O*-phenyl- $\beta$ -D-glucopyranoside ( $\beta$ -phenylglucose).

#### 2. *Disaccharides*

3-*O*- $\beta$ -D-galactopyranosyl-D-arabinopyranoside; 1-*O*- $\beta$ -D-mannopyranosyl-L-erythritol; 4-*O*- $\beta$ -D-galactopyranosyl-D-glucopyranoside (lactose); 6-*O*- $\alpha$ -D-galactopyranosyl-D-glucopyranoside (melibiose); 1-*O*- $\alpha$ -D-glucopyranosyl-

$\beta$ -D-fructofuranoside (sucrose); 3-O- $\alpha$ -D-glucopyranosyl-D-fructopyranoside (turanose); 1-O- $\alpha$ -D-glucopyranosyl- $\alpha$ -D-glucopyranoside (trehalose); 4-O- $\alpha$ -D-glucopyranosyl-D-glucopyranoside (maltose); 4-O- $\beta$ -D-glucopyranosyl-D-glucopyranoside (cellobiose); 6-O- $\beta$ -D-glucopyranosyl-D-glucopyranoside (gentiobiose).

### 3. Disaccharide Derivatives and Disaccharide Glycosides

4-O- $\alpha$ -D-glucopyranosyl-D-glucopyranoside-1,2,2',3,3',4',6,6'-octaacetate (maltose octaacetate); 4-O- $\beta$ -D-glucopyranosyl-D-glucopyranoside-1,2,2',3,3',4',6,6'-octaacetate, (cellobiose octaacetate); 1-O- $\alpha$ -D-glucopyranosyl- $\alpha$ -D-fructofuranoside-1,2',3,3',4,4',6,6'-octaacetate (sucrose octaacetate); 1-O- $\beta$ -phenyl-(4-O- $\beta$ -D-galactopyranosyl)-D-glucopyranoside ( $\beta$ -phenyllactose).

### 4. Higher Oligosaccharides

1-O- $\alpha$ -D-galactopyranosyl-(1  $\rightarrow$  6)-O- $\alpha$ -D-glucopyranosyl-(1  $\rightarrow$  2)- $\beta$ -D-fructofuranoside (raffinose); 1-O- $\alpha$ -D-glucopyranosyl-(1  $\rightarrow$  3)-1-O- $\beta$ -D-fructofuranosyl-(2  $\rightarrow$  1)- $\alpha$ -D-glucopyranoside (melezitose); 1-O- $\beta$ -D-glucopyranosyl-(1  $\rightarrow$  3)- $\beta$ -D-glucopyranosyl-(1  $\rightarrow$  4)-D-glucopyranoside; 1-O- $\alpha$ -D-galactopyranosyl-(1  $\rightarrow$  6)- $\alpha$ -D-galactopyranosyl-(1  $\rightarrow$  6)-1- $\alpha$ -D-glucopyranosyl-(1  $\rightarrow$  2)- $\beta$ -D-fructofuranoside (stachyose); 1-O- $\beta$ -( $\delta$ -20:22-3 $\beta$ -O-12 $\beta$ -14,21-tetrahydroxynorcholenic acid lactone)-1-O- $\beta$ -D-2,6-dideoxyribopyranosyl-(1  $\rightarrow$  4)- $\beta$ -D-2,6-dideoxyribopyranosyl-(1  $\rightarrow$  4)-D-2,6-deoxyribopyranoside (digoxin); 1-O- $\beta$ -( $\delta$ 20:22-3 $\beta$ -O-14,21-trihydroxynorcholenic acid lactone)-1-O- $\beta$ -D-2,6-dideoxyribopyranosyl-(1  $\rightarrow$  4)- $\beta$ -D-2,6-dideoxyribopyranosyl-(1  $\rightarrow$  4)-D-2,6-dideoxyribopyranoside (digitoxin); 1-O- $\beta$ -( $\delta$ -20:22-3-O-14,16,21-tetrahydroxynorcholenic acid lactone)-1-O- $\beta$ -D-2,6-dideoxyribopyranosyl-(1  $\rightarrow$  4)- $\beta$ -D-2,6-dideoxyribopyranosyl-(1  $\rightarrow$  4)-D-2,6-dideoxyribopyranoside (gitoxin); 1-O- $\beta$ - $\delta$ 20:22-3-O,14,21-trihydroxy-16-formyl norcholenic acid lactone)-1-O- $\beta$ -D-dideoxyribopyranosyl-(1  $\rightarrow$  4)- $\beta$ -D-2,6-dideoxyribopyranosyl-(1  $\rightarrow$  4)-D-2,6-dideoxyribopyranoside (gitaloxin); 1-O- $\beta$ -D-(5 $\alpha$ ,22a,25a-spirosterane-2 $\alpha$ ,3 $\beta$ -O,15 $\beta$ -triol)-1-O- $\beta$ -D-xylopyranosyl-(1  $\rightarrow$  3)- $\beta$ -D-glucopyranosyl-(1-O- $\beta$ -D-glucopyranosyl-(1  $\rightarrow$  3)- $\beta$ -D-galactopyranosyl-(1  $\rightarrow$  2))-(1  $\rightarrow$  4)-D-galactopyranoside (digitonin); 1-O- $\beta$ -(3 $\beta$ -O-16-oxoholosta- $\delta$ 9:11,25-diene)-3-O-methyl- $\beta$ -D-glucopyranosyl-(1  $\rightarrow$  4)- $\beta$ -D-quinovopyranosyl-(1  $\rightarrow$  3)- $\beta$ -D-glucopyranosyl-(1  $\rightarrow$  2)-D-xylopyranoside-6'-O-6'''-O-disodium disulfonate (psoluthurin A); 1-O- $\beta$ -(3 $\beta$ -O-23-acetoxylolost-7-ene)-3-O-methyl- $\beta$ -D-glucopyranosyl-(1  $\rightarrow$  4)- $\beta$ -D-xylopyranosyl-(1  $\rightarrow$  3)- $\beta$ -D-quinovopyranosyl-(1  $\rightarrow$  3)- $\beta$ -D-xylopyranosyl-(1  $\rightarrow$  2)-D-xylopyranoside-4-O-sodium sulfonate (frondoside A).

Figure 8 depicts all the monosaccharide units discussed in this article.

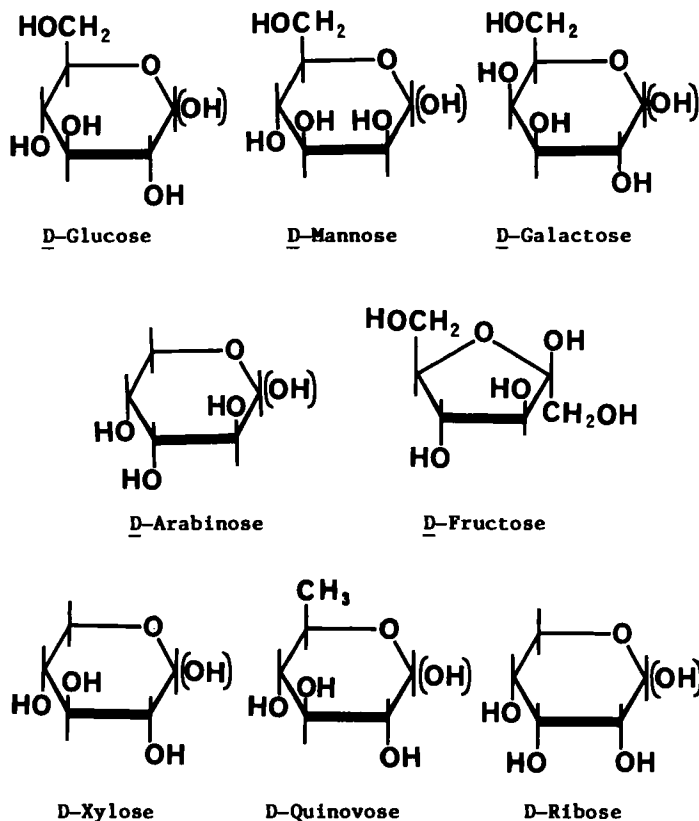


FIG. 8. Monosaccharide units present in the polysaccharides used in this study.

#### D. MONOSACCHARIDE GLYCOSIDES

Tables I–III give some selected<sup>3</sup> FAB data for anomeric pairs of monosaccharide glycosides in the positive ion mode. Differences occur in the mass spectral data recorded within a given anomeric pair and this is true for every pair studied.

The FAB mass spectra of the methylglucose pair have features that can be interpreted in terms of their stereochemical properties.  $\beta$ -Methylglucose, for example, exhibits a much larger proton affinity than the  $\alpha$  anomer yielding a much more intense pseudomolecular ion at  $m/z$  195.

<sup>3</sup> Full spectra for all original data are available from the authors (JRJP) upon request or from (84TH2)

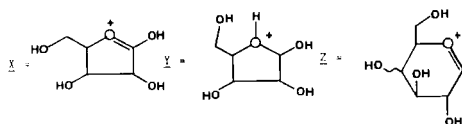
TABLE I  
SELECTED FAB-MS DATA (%I) OF 1-O-METHYL-D-GLUCOSE<sup>a</sup>

<i>m/z</i>	Ion	$\alpha$	$\beta$
127	$[163 - 2(\text{H}_2\text{O})]^+$	42.0	39.3
145	$[163 - \text{H}_2\text{O}]^+$	88.7	92.7
163	$[\text{M} + \text{H} - \text{CH}_3\text{OH}]^+$	86.7	100.0
183	?	25.1	13.7
193	$[\text{M} - \text{H}]^+$	14.0	17.4
194	$[\text{M}]^+$ (isotopic for 193)	2.7	—
195	$[\text{M} + \text{H}]^+$	18.7	46.5
217	$[\text{M} + \text{Na}]^+$	4.7	14.3
255	$[\text{M} + \text{gly} + \text{H} - \text{CH}_3\text{OH}]^+$	88.0	64.3
287	$[\text{M} + \text{gly} + \text{H}]^+$	100.0	50.4
325	$[2\text{M} + \text{H} - 2(\text{CH}_3\text{OH})]^+$	17.7	21.1
357	$[2\text{M} + \text{H} - \text{CH}_3\text{OH}]^+$	11.5	11.8
377	?	5.4	1.1
379	$[\text{M} + 2\text{gly} + \text{H}]^+$	6.1	—
389	$[2\text{M} + \text{H}]^+$	35.4	30.8
481	$[2\text{M} + \text{gly} + \text{H}]^+$	3.2	—

<sup>a</sup> Positive ions in glycerol; corrected for matrix background; —, not detected.

TABLE II  
SELECTED FAB-MS DATA (%I) OF 1-O-PHENYL-D-GLUCOSE<sup>a</sup>

<i>m/z</i>	Ion	$\alpha (\text{H}_2\text{O})^b$	$\beta$
127	$[163 - 2\text{H}_2\text{O}]^+$	36.5	26.6
145	$[163 - \text{H}_2\text{O}]^+$	81.9	64.7
149	X	25.8	36.1
151	Y	19.2	28.3
163	Z	67.7	51.2
255	$[\text{M} - \text{H}]^+$ and $[163 + \text{gly}]^+$	100.0	100.0
256	Isotopic of 255	15.8	11.8
257	$[\text{M} + \text{H}]^+$	3.8	5.8
325	$[2\text{M} + \text{H} - 2(\text{C}_6\text{H}_5\text{OH})]^+$	20.0	10.7
349	$[\text{M} + \text{gly} + \text{H}]^+$	50.8	43.1
441	$[\text{M} + 2\text{gly} + \text{H}]^+$	7.3	14.7
513	$[145 + 4\text{gly}]^+$	11.5	4.9
533	$[\text{M} + 3\text{gly} + \text{H}]^+$	—	3.2
605	$[145 + 5\text{gly}]^+$	—	3.2



<sup>a</sup> Positive ions in glycerol; corrected for matrix background; —, not detected.

<sup>b</sup> ( $\text{H}_2\text{O}$ ) indicates spectra recorded in a glycerol/water mixture.

TABLE III  
SELECTED FAB-MS DATA (%I) OF 1-*O*-*p*-NITROPHENYL MONOSACCHARIDES<sup>a</sup>

<i>m/z</i>	Ion <sup>b</sup>	Galactose		Glucose	
		$\alpha$	$\beta$	$\alpha$ (H <sub>2</sub> O)	$\beta$
123		100.0	35.3	92.4	63.3
124		77.8	23.5	65.5	56.1
127	(163 – 2H <sub>2</sub> O) <sup>+</sup>	20.4	—	23.5	15.3
139		—	—	5.9	5.1
140		61.1	23.5	56.3	29.6
145	(163 – H <sub>2</sub> O) <sup>+</sup>	44.4	—	63.9	34.7
149	X	72.2	100.0	100.0	100.0
151	Y	61.1	70.6	79.8	90.8
163	Z	94.4	32.4	37.8	21.4
209		57.4	82.4	55.5	68.4
215	(123 + gly) <sup>+</sup>	—	—	22.7	20.4
255	(163 + gly) <sup>+</sup>	51.9	26.5	38.7	26.5
285		25.9	—	27.7	13.3
301	(M) <sup>+</sup>	13.0	20.6	14.3	16.3
302	(M + H) <sup>+</sup>	16.7	—	19.3	9.2
394	(M + gly + H) <sup>+</sup>	55.6	44.1	36.1	18.4
486	(M + 2gly + H) <sup>+</sup>	13.0	—	—	10.2

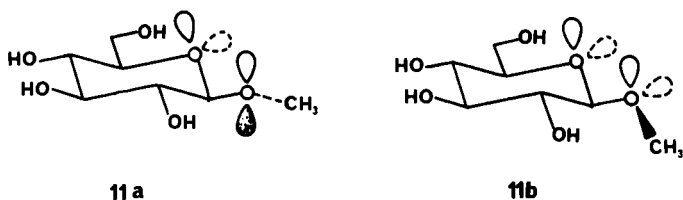
<sup>a</sup> Positive ions in glycerol; corrected for matrix background; —, not detected.

<sup>b</sup> For structures X, Y, and Z refer to Table II.

<sup>c</sup> (H<sub>2</sub>O) indicates spectra recorded in a glycerol/water mixture.

Consequently the peaks at *m/z* 163, the pyranoxonium ion (ring oxygen) (see structure Z, Table II) resulting from the loss of methanol (from *m/z* 195) (78OMS51), *m/z* 145, and *m/z* 127, the sequential losses of two water molecules from *m/z* 163, are also more prominent for the  $\beta$  anomer. A more intriguing and promising feature is the very intense peak at *m/z* 287 in the  $\alpha$  anomer that is present to a much lesser extent in the  $\beta$  counterpart. That particular peak corresponds to the cluster of one protonated glycoside molecule attached to a glycerol molecule. The reason for such a discrepancy is not obvious and it is believed to be stereochemically related. It has been shown that  $\beta$ -methylglucose exists in a single rotameric state (depicted as **11a**) because both steric and electronic effects favor such a conformer (82CJC1067). In fact, this can be explained in terms of steric factors, assuming that the lone pairs are considered bigger or nearly equal in size to the hydrogens (a matter of controversy) (75MI5; 79MI5) and, for this system, of the more important electronic component, the *exo*-anomeric effect (69CJC4427; 69T3365; 75TL4339; 76JA3583; 81MI10; 82CJC1067). That favored conformer **11a** seriously restricts the binding of glycerol to the sugar unit through the ring

oxygen and those at C-1 and C-6 because the lone pairs of the oxygen are not both in the upper conformation. Rotamer **11b** could allow for better glycerol binding, but it has been shown not to exist, or to be present only to limited extent. This phenomenon occurs only in  $\beta$ -glycosides, thus  $\alpha$ -methylglucose exists as several rotamers (around the glycosidic bond), some of which must favor the binding to the glycerol moiety. Molecular models show that no rotamer for any  $\alpha$ -glycoside favors binding through the glycosidic oxygen, which is necessary to account for the low production of ions at  $m/z$  163 and large production of ions at  $m/z$  287. However, if the glycosidic oxygen is protonated and the glycerol unit attached via that same hydrogen, it yields an aggregate species that accounts for both the intense peak at  $m/z$  287 (binding to glycerol via a proton through the oxygens at C-1, C-2, and C-3) and the reduced peak, with respect to the  $\beta$  anomer, at  $m/z$  163. All of these findings strongly suggest the fact that protonation must occur at the glycosidic oxygen, which is in agreement with a previous report based on FD studies (81LA683).



The negative-ion FAB spectra of the methylglucose glycosidic pair show complementary features; a glycerol adduct at  $m/z$  286 being again much greater in the  $\alpha$  anomer.

The FAB mass spectra for the phenylglucose pairs (Table II) do not show substantial differences, but for the various protonated molecular species—glycerol adducts at  $m/z$  349, 441, and 533 whose intensities vary between the anomers (greater for  $\beta$ ) and for an unusual peak at  $m/z$  325 that is defined as  $[2M + H - 2(C_6H_5OH)]^+$  by comparison to the disaccharide analysis reported below. A very interesting feature, however, is the peak at 255 that can be attributed to two ions,  $[M - H]^+$  and  $[163 + \text{glycerol}]^+$ . The former can result either from the abstraction of a hydrogen radical or the oxidation (loss of  $H_2$ ) of the normally expected  $[M + H]^+$  species at  $m/z$  257 which is only weakly present.

It is suggested that  $m/z$  255 corresponds to the  $[M - H]^+$  ion. This statement is based upon complementary information obtained from negative-ion spectra, where the molecular anion (or anion radical?) is recorded ( $m/z$  256) instead of the standard  $[M - H]^-$  ion. Furthermore,  $B^2/E$  linked scans (82SIJ169) were performed on a similar  $[M - H]^+$  peak found in ergosterol

(84UP1) and thus established that the origin of the peak was not  $[M + \text{glycerol} + H]^+$  necessary to produce  $[163 + \text{gly}]^+$ .

The two anomers present only one difference in their negative-ion FAB spectra, namely a reversal in the intensities of two ions at  $m/z$  120 and 162. This phenomenon can also be accounted for in terms of stereochemical effects. For this pair, steric hindrance is seen as the most important factor affecting the stability of the  $[M]^-$  ion. Clearly the rotation of the phenyl moiety around the glycosidic bond and around the O—C1' bond is more difficult for the  $\beta$  anomer. Charging the phenyl ring with an extra negative charge increases further its molecular geometry and imposes a stress sufficient to yield an intense peak at  $m/z$  162 resulting from the loss of a phenol unit (kinetic control) thus reducing the probability of producing the ion at  $m/z$  120 which requires a fission of the carbohydrate ring. The  $\alpha$  anomer on the other hand does not suffer to the same extent from such an enhanced steric factor, since for some rotamers the phenyl ring does not overlap with the carbohydrate ring. Formations of  $m/z$  120 (thermodynamic control) is therefore not inhibited, although not necessarily favored either.

Finally, Table III presents the data for the *p*-nitrophenylgalactose and the *p*-nitrophenylglucose pairs. The addition of a nitro group to the phenyl ring did not only enlarge it, but also enhanced the overall dipole moment exerted by the aglycone on the carbohydrate residue. This results in a much more extensive overall fragmentation.

This series also allows for a first glance at the effect of changing the stereochemistry at C-4 of the carbohydrate moiety. Comparisons can then be drawn within a pair and between the pairs for a given configuration. Differences within a pair are again evident and they are more numerous here. In the positive ion spectra, major variations are present throughout the spectra. Peak relative intensities for ions at  $m/z$  123, 127, 140, 145, 163, 285, and 302 are especially noteworthy. They all are larger for the  $\alpha$ -anomers. The first five indicate the greater instability of the  $\alpha$ -anomer, which was known to be the case in terms of the lesser strength of the glycosidic bond. These fragments come from a fission at the glycosidic bond ( $m/z$  163, 145, and 127) creating an oxonium ion within the carbohydrate ring (structure Z, Table II) or from the fission of the ring ( $m/z$  123 and 140). The ions at  $m/z$  285 and 302 indicate a greater proton affinity for the  $\alpha$  anomer. Another result of great significance is the variation in the ionic intensities of  $m/z$  163 and 215 between the galactosyl and the glucosyl residues. To obtain  $m/z$  163 it is necessary to "hydrolyze" *p*-nitrophenol from the  $[M + H]^+$  species. If, however, a glycerol unit binds through the glycosidic oxygen, as it is favored in the  $\beta$  anomers, then production of  $m/z$  163 is greatly hindered. Furthermore, the  $\alpha$  configuration offers the proper stereochemical arrangement for a stereoelectronically controlled elimination of the molecular aglycone (76MI10). This factor, i.e.,

glycerol adduct formation via the glycosidic bond, is thought to be of prime importance and, as will be discussed later, it plays a role that makes it one of the three leading factors governing the fragmentation pattern of glycosides and the like. The peak at  $m/z$  215 in turns indicates a greater facility for the galactosyl moiety to bind to a glycerol through oxygens other than the glycosidic one ( $m/z$  215 is the adduct of ion of mass 123 attached to a glycerol unit). This is related to the stereochemistry at C-4; it is seen here as a remote stereochemical effect. The corresponding negative ion spectra provide complementary evidence for these explanations.

From this preliminary review of monosaccharide glycosides, it is possible to see that the fragmentation pattern in FAB mass spectra is governed by at least three factors whose importance may vary: (1) nature of the aglycone, (2) configuration of the anomeric carbon; (3) remote stereochemical effects (i.e., the relative stereochemistry of the other carbohydrate carbons).

To further substantiate and to better understand and evaluate these primary factors, it is necessary to analyze several other spectra of model compounds in terms of stereochemical factors. A series of intact disaccharides should be most appropriate for that purpose.

## E. DISACCHARIDES

Very little work appears to have been published to date on stereochemical considerations in carbohydrates using FAB-MS. In fact we were able to find only two reports dealing with a variation in fragmentation patterns due to the stereochemistry of the glycosidic bond and these involve some simple monosaccharide glycosides studied under FD conditions (73OMS1103; 81ABC1505). Two other reports deal with stereochemical implications of FAB data of monosaccharide units (83BMS512; 84SIJ155). Finally, two reports from our laboratories should be among the first to underline the potential of the technique as a stereochemical probe (87UP1; 87UP2). Consequently, we here introduce some original data, along with supporting and related literature, on FAB-MS of carbohydrates. These are representative of the state of the field as it stands today.

It is impossible to present these results without a word of caution. To understand and fully evaluate, say, the remote stereochemistry factor, one would need to record an almost limitless number of combinations and permutations of hydroxyl moieties at one, the other, or several carbons at once. Clearly this would be outside the scope of a report such as this one. We are blessed, however, by the fact that there does not appear to be any major fragmentation attributable to the reducing end of the disaccharides so that the stereochemistry of the reducing sugar is of little importance, except for the fact



that the reducing sugar competes directly with its nonreducing counterpart for the binding to a glycerol moiety. This brings in a fourth factor of major importance, and probably the most important one, the *nature of the matrix* (whether it is used as a support, a matrix, or a solvent). This will be discussed in more detail during the course of this subsection and the following ones. Because of the limitations imposed by a large number of possibilities for the disaccharides, only a few representative species have been selected. The choice was made according to the need for some variety (to show extent of applicability) and for a stereochemical relation between the chosen species (e.g.,  $\alpha$  and  $\beta$  anomers of a given disaccharide arrangement). The availability of the disaccharides was also considered, since they are to be used as models.

Furthermore, only the positive-ion FAB mass spectra will be discussed; this will be done on a group basis, rather than individually, as it was the case for the monosaccharide glycoside section just preceding. Data obtained from negative-ion spectra and recorded in various support matrices will only be used as complementary information. It is clear, however, that the latter will attract more attention in the future.

Dell and co-workers presented earlier some overall fragmentation patterns involving the glycosidic bond (83BMS50; 83MI1). Their report, based upon a study of large polysaccharides, did not suggest any mechanisms for the formation of the proposed ion structures. Figure 9 presents the mechanisms for the three main patterns they reported (83MI1), along with a fourth one,

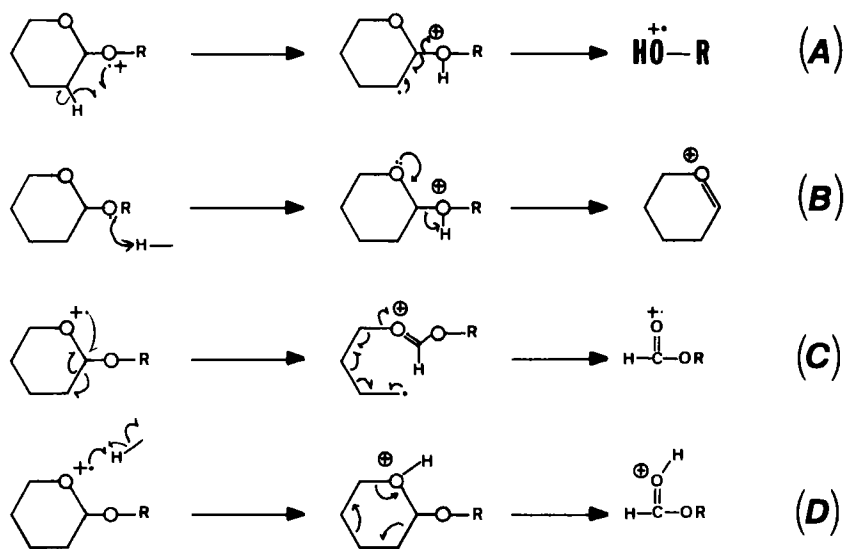


FIG. 9. Fragmentation patterns of the glycosidic bond under FAB conditions in the positive ion mode.

closely related, introduced here for the first time and which accounts for major peaks in the spectra. The information contained in their report is limited by the fact that the carbohydrate units making up the polysaccharide used in their study were almost exclusively of the  $\alpha$  configuration, and were glycosides themselves as they bear some methyl moieties on O-6, an "artificial" case, too specific to be used a general guideline, but a good reference point to direct further work.

Before discussing the main features of the spectra in terms of stereochemical concepts, let us review some conformational principles in oligosaccharide chemistry, more specifically in disaccharides. It will then be possible to relate the salient points of the spectra directly to these conformational principles.

Discussion of the overall shapes of carbohydrate chains usually starts from knowledge of, or assumptions about, the conformations of the component sugar rings (65MI1; 75MI5; 77MI9). Since six-membered (pyranose) rings are by far the most common in naturally occurring polysaccharides and their individual ring conformations are more stable and well defined, most of the successful work has been done with those systems. The only major exceptions are in the field of polynucleotides, for which the interconversion between furanose conformations plays an important role in the determination of the polymer form.

The pyranose ring conformations that are important in polysaccharides are the two chair conformations, designated  ${}^4C_1$  and  ${}^1C_4$  (Fig. 10) to indicate the disposition of atoms above and below the plane of the ring (in older notation the same conformations were denoted by C1 and 1C, respectively). Boat conformations probably have some existence in low proportions in disordered (random coil) polysaccharide chains.

The approaches available for predicting the relative stabilities and hence equilibrium populations of alternative conformations have been thoroughly reviewed (65MI1; 75MI5), and for free sugars this can extend to comparison of the relative stabilities of alternative isomers, such as five-membered (furanose) rings or open chains. They begin from two complementary, but quite different approaches.

1. Measurement of equilibrium constants are used empirically to derive the corresponding free energies (68AJC2737; 69AG(E)157).

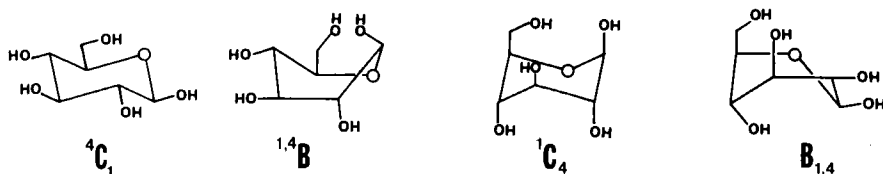


FIG. 10. Pyranoside ring conformation (illustrated for  $\beta$ -D-glucose).

2. In a more general approach, attempts are made to build up a complete picture of all the actual attractions and repulsions between atoms in terms of van der Waals forces, polar interactions, hydrogen bonding, and torsional contributions (75JCS(P2)830; 77JCS(P2)654).

The calculations are now refined to a point at which an accurate prediction can usually be made of the conformations that will predominate in sugar solutions, as well as the proportions of each form. They may even indicate minor distortions and deviations from "ideal" chair geometry, although they make no attempt to consider terms involving solvent. It appears that these terms usually cancel when differences in free energy are considered, but exceptions are known in which additional stabilization of particular conformations by water is indicated. In general, however, the shape of naturally occurring pyranose rings in carbohydrate chains may be regarded as fixed in that chair conformation in which C-6 is equatorial ( ${}^4C_1$  for D sugars and  ${}^1C_4$  in the L series). Overall chain geometry is therefore determined predominantly by the relative orientations of adjacent residues.

For glycosidic bonds in which linkage is through an oxygen atom attached to a ring carbon, the relative orientations of the participating residues can be defined completely by the two dihedral angles  $\phi$  and  $\psi$  (by analogy to peptides) shown in Fig. 11. When the connecting linkage is between C-1 of one residue and C-6 of its neighbor, there is an extra covalent bond and torsion angle ( $\omega$ ), giving these units markedly increased freedom to adopt a wide variety of orientations relative to each other. The term *linkage conformation* (73MI5) is used to define a distinct set of values for these angles ( $\phi$ ,  $\psi$ ) or ( $\phi$ ,  $\psi$ ,  $\omega$ ).

In considering the overall conformations of carbohydrate chains it is useful to start by distinguishing between (1) ordered conformations, in which the values of the torsion angles are fixed by cooperative interactions between residues; and (2) disordered conformations, in which continuous fluctuation occurs.

It is not possible to deal with linkage geometry in polysaccharides by simple extension of the classical methods for conformational analysis of small molecules, since we would first have to identify a limited number of discrete conformations that correspond to the important low-energy forms in equilibrium. The alternative approach is to calculate conformational energies directly from energy functions by listing the stereochemical constraints that have been established from structural studies. The computer methods used to do this have been reviewed extensively (68APO103; 68MI5; 68MI6; 69MI1; 71CRV195; 73MI5).

One source of unambiguous information on the rotational angles between adjacent sugar residues consists of X-ray diffraction studies of crystalline disaccharides and their derivatives. These may then be compared with values

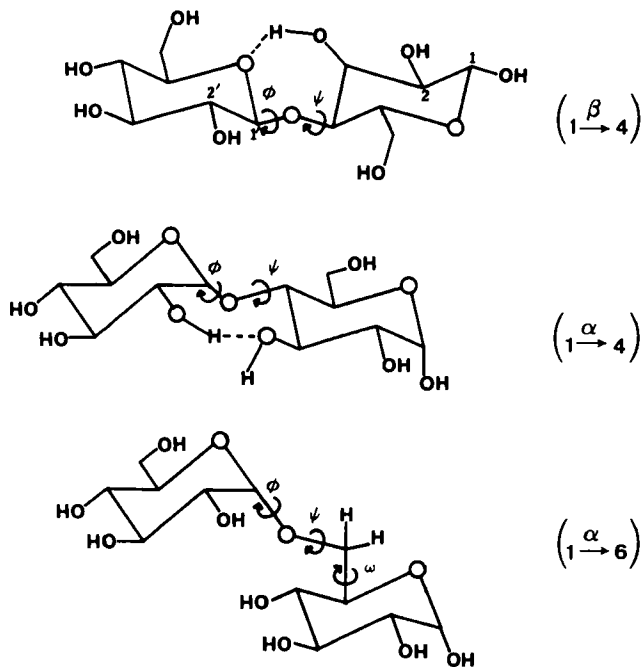


FIG. 11. Interresidue linkages in carbohydrates chains (illustrated for some glucose dimers). Linkage conformation is defined by the dihedral angles ( $\phi$ ,  $\psi$ ) or ( $\phi$ ,  $\psi$ ,  $\omega$ ). The intramolecular hydrogen bonds are also indicated.

predicted from calculation. Irrespective of the method of conformational analysis employed, the strategy is to develop a map showing the variation of internal energy with rotation around the glycosidic angles  $\phi$  and  $\psi$  (Fig. 11). Except for (1  $\rightarrow$  6)-linkages, all such calculations show that more than 90% of the conformations on the map are energetically disallowed (75JCS(P2)836).

For cellobiose and maltose and derivatives, a sufficient number of crystal structures have been determined to allow useful comparisons to be made (73MI5; 75JCS(P2)836). It was shown that on the map obtained for cellobiose (73JCS(P2)836) different forms do not have exactly the same conformation at the glycosidic linkage, but lie close together within the predicted boundary and very close to the overall minimum of the energy map. Presumably, the slight adjustments from one derivative to another occur to facilitate packing in a different crystal environment. Although the cellobiose map shows two troughs of favored conformational energy, only one of these is populated. This zone is larger in area and hence more "probable" than the smaller area; it also contains zones of somewhat lower energy states and allows the formation of a hydrogen bond between O-3 on one residue and O-5 on an adjacent

one. Interpretations of optical rotation studies (77JCS(P2)191) in dimethyl sulfoxide and water in terms of contributions to the overall optical rotation from the linkage conformation also show good agreement between the observed values and those calculated from the solid-state conformation. This agreement does not imply that the disaccharide in solution is locked in the crystal conformation, but it does suggest a preference for  $\phi$  and  $\psi$  values in the neighborhood of the minimum energy conformation.

Analogous calculations (73MI5; 75JCS(P2)836) for maltose show that the crystal conformations characterized by X-ray diffraction are more scattered, but again lie mainly in a single zone around the minimum energy conformation, which is once more stabilized by a hydrogen bond between the two sugar rings. A consequence of the difference in configuration at C-1 between cellobiose and maltose is that the stabilizing hydrogen bond is between different pairs of oxygen atoms. In maltose it is between O-3 of one residue and O-2 of its neighbor (Fig. 11).

In contrast to cellobiose, optical rotation measurements in solution (77JCS(P2)191) indicate that maltose does not always oscillate in the neighborhood of the hydrogen-bonded conformation. This linkage conformation is very close to eclipsed positions about both bonds to the glycosidic oxygen, and, although the O-2 $\cdots$ O-3' hydrogen bond evidently offsets this disadvantage in the solid state, this is not possible in strongly hydrogen-bonded solvents. In dioxane and dimethyl sulfoxide, both optical rotation and proton nuclear magnetic resonance ( $^1\text{H}$  NMR) measurements (68T803; 70MI2; 76JA4386) suggest that, although the time-averaged conformation is significantly displaced from the crystal structure, a large proportion of molecules exist in the major zone in which the hydrogen bond is possible. In aqueous solution, by contrast, the evidence suggests that the molecule must spend a much larger portion of its time in the area of the subsidiary minimum. Carbon-13 NMR observations (70CJC3745) confirm that in water steric or proximity effects occur between the sugar residues, as would be expected for the alternative "folded" structure. It is also possible that the arrangement of sugar hydroxyl groups in the alternative zone matches more closely the organization in transiently ordered "clusters" of water molecules to provide the extra stability that the conformational calculations fail to predict (77JCS(P2)191). The solvent dependence of conformation seen in maltose, however, appears to be a relatively uncommon effect.

For some linkages, at least, it is possible to detect a substantial influence on the rotation about the glycosidic bond from the exo anomeric effect; this evidence is from  $^{13}\text{C}$ - $^1\text{H}$  coupling constants (74T1933; 80CJC631) and optical rotation techniques (71JCS(B)469).

For diequatorial linkages, calculations show that the numerically averaged values of  $\phi$  and  $\psi$  can be predicted independently,  $\phi$  being determined by the

size of the equatorial substituent in C-2' and  $\psi$  by those in C-3 and C-5. On this basis, groups of glucosyl oligomers, for example, could then be assigned the value of  $\phi$  known for cellobiose from both solution and crystal studies, whereas that of lactose could be applied to galactosyl homologues, and the measured optical rotations then analyzed to calculate the values of  $\psi$  (71JCS(B)469). For a large number of compounds, the results demonstrated with remarkable consistency that (1) each group of oligosaccharides having a similar substitution around the aglycone bond shows only very small variations in  $\psi$ , and (2) replacement of a substituent with a less bulky one causes  $\psi$  to shift as expected toward the extra space that is created.

The factors affecting  $\phi$  and  $\psi$  for  $\alpha$  linkages are more interdependent, but a similar general picture emerges if it is assumed that, as in the  $\beta$  series,  $\phi$  is the same for all related compounds. Conformational analysis also shows that increasing the number of axial linkages to the glycosidic oxygen decreases the number of accessible conformations.

With these basic conformational principles it is now possible to account for the difference in the fragmentation patterns of a series of disaccharides presented in Table IVa–IVd. The first major difference lies in the presence of a ring oxonium ion (mechanism B, Fig. 9) that seems to occur to a much larger extent in the  $\alpha$ -linked disaccharides. This can be accounted for by the fact that in order to produce that fragment ion, the lone pair of the ring oxygen (O-5') must be able to assist in the elimination of the reducing sugar (this is strictly speaking the analog of a simple hydrolysis reaction under mild acidic conditions). The stereoelectronic effects (anomeric effect) clearly favor this pathway for  $\alpha$  configuration nonreducing sugar. Furthermore, in  $\beta$ -linked (1  $\rightarrow$  4)-disaccharides it was just established that the interresidue hydrogen bonding was involving the lone pair of electrons of O-5' of the nonreducing end (Fig. 11); these electrons are therefore less able to assist the elimination process as they are already partially localized. This fragmentation can therefore be explained in terms of (1) the configuration of the anomeric carbon, as per Fig. 10, and (2) the remote stereochemistry factor.

Inherently, the nature of the aglycone was primordial in allowing intramolecular hydrogen bond formation. For example, the case of  $\beta$ -D-galactopyranosyl-(1  $\rightarrow$  3)-D-arabinoside (Table IVa, column 2) depicts the potential of the technique. In fact, at first sight this disaccharide seems not to follow the trend that was just established as it is a  $\beta$ -linked disaccharide, and yet it exhibits the oxonium ion (at  $m/z$  163) as its base peak. However, if consideration is taken of the fact that this is a (1  $\rightarrow$  3)-linkage and that the stereochemistry at C-3 and (C-2) of D-arabinoses are inverted, it should then be expected that intramolecular hydrogen bonding via the galactosyl O-5 is impossible, thus enabling the lone pair to assist in the elimination of the arabinose residue. In fact, now the spectrum exhibits two peaks of nearly equal

TABLE IVa  
SELECTED POSITIVE-ION FAB-MS DATA (%I) OF SOME DISACCHARIDES<sup>a</sup>

<i>m/z</i>	1- <i>O</i> -β-D-Mannopyranosyl- L-erythritol [gly/H <sub>2</sub> O]	3- <i>O</i> -β-D-Galactopyranosyl- D-arabinopyranoside [gly/H <sub>2</sub> O]
103	6.5	27.2
115	29.7	70.4
122	—	—
123	100.0	16.7
127	9.6 (B)	18.5 (B)
131	4.8	21.1
133	8.3	92.0 (A)
145	12.0 (B)	39.5 (B)
149 (X)	13.9	47.5
150	1.0 (C)	6.8 (A)
151 (Y)	15.6 (D)	51.2
163 (Z)	24.1 (B)	100.0 (B)
178	—	— (C)
179	—	4.3 (D)
207	12.7	14.8
215	5.5	8.6
241	4.9	18.5 [149 + gly] <sup>+</sup>
243	4.4	17.9 [151 + gly] <sup>+</sup>
259	1.5	22.8
285	78.6 [M + H] <sup>+</sup>	—
295	—	75.3 [M + H - H <sub>2</sub> O] <sup>+</sup>
313	—	79.6 [M + H] <sup>+</sup>
377	9.6	—
387	—	6.2 [M + gly + H - H <sub>2</sub> O] <sup>+</sup>
405	—	46.9 [M + gly + H] <sup>+</sup>
469	1.9	—
497	—	6.8 [M + 2gly + H] <sup>+</sup>
561	0.9 [M + 3gly + H] <sup>+</sup>	—
569	7.6 [2M + H] <sup>+</sup>	—
589	—	6.2 [M + 3gly + H] <sup>+</sup>
607	—	2.5 [2M + H - H <sub>2</sub> O] <sup>+</sup>
625	—	9.9 [2M + H] <sup>+</sup>

<sup>a</sup> See footnote at bottom of Table IVd.

intensities at *m/z* 133 and *m/z* 163, corresponding to mechanisms A and B, respectively (Fig. 9).

This effect, the remote stereochemistry factor, is also responsible for the differences between a given galactosyl versus glucosyl pair of disaccharides (e.g., lactose and cellobiose, Table IVb, column 1, and Table IVd, column 3, respectively). With the only primary difference residing in the stereochemistry at C-4 of the nonreducing end of the disaccharide (according to the previously

TABLE IVb  
SELECTED POSITIVE-ION FAB-MS DATA (%I) OF SOME DISACCHARIDES<sup>a</sup>

<i>m/z</i>	Ion	Lactose		Melibiose	
		[gly]	[gly/H <sub>2</sub> O]	Monohydrate [gly]	Dihydrate [gly]
105	[123 - H <sub>2</sub> O] <sup>+</sup>	22.2	24.2	11.1	25.7
123		69.3	59.8	21.4	77.4
127	(B)	16.4	33.0	37.6	18.8
145	(B)	30.5	48.0	56.4	37.0
149	X	100.0	54.9	17.9	89.7
151	Y	86.5	46.2	15.8	77.6
153		55.2	42.9	14.4	61.5
163	(B) Z	68.1	100.0	100.0	69.1
180	(A)	—	2.8	1.8	2.6
183		95.6	60.5	18.8	100.0
208	(C)	3.9	2.1	1.0	3.2
209	(D)	72.0	25.9	6.9	47.4
215	[123 + gly] <sup>+</sup>	59.2	32.2	6.0	61.6
241	[149 + gly] <sup>+</sup>	56.1	19.7	4.3	39.1
243	[151 + gly] <sup>+</sup>	39.6	14.8	3.5	29.4
245	[153 + gly] <sup>+</sup>	32.9	17.2	3.4	35.8
255	[163 + gly] <sup>+</sup>	15.0	12.4	15.8	25.2
273	[180 + gly + H] <sup>+</sup>	11.2	8.5	3.3	12.4
275	[183 + gly] <sup>+</sup>	40.6	16.6	3.0	40.0
307	[M + H - 2H <sub>2</sub> O] <sup>+</sup>	13.5	6.2	3.5	13.1
325	[M + H - H <sub>2</sub> O] <sup>+</sup>	30.2	33.4	30.9	28.3
343	[M + H] <sup>+</sup>	74.2	68.8	17.5	33.5
417	[M + gly + H - H <sub>2</sub> O] <sup>+</sup>	—	1.8	1.3	2.8
435	[M + gly + H] <sup>+</sup>	18.6	10.4	4.8	31.4
527	[M + 2gly + H] <sup>+</sup>	6.2	22.0	—	3.9
685	[2M + H] <sup>+</sup>	—	5.1	4.8	—

<sup>a</sup> See footnote at bottom of Table IVd.

presented conformational principles, these two disaccharides should exhibit the same overall conformation, i.e., that depicted in Fig. 11), any variation in the fragmentation pattern might be attributable to that stereochemical difference. In the pair just mentioned, there are a few differences. For example, *m/z* 163 (Mechanism B, Fig. 9) is of low intensity in cellobiose and of somewhat higher intensity for lactose. This can also be accounted for in terms of the nature of the matrix. In fact, it is possible to attach a glycerol unit through the oxygen atom at C-3, C-4, and C-6 of the galactosyl residue (but not for the glucosyl one), thus distorting the overall conformation of the glycerol-hydrogen-disaccharide adduct so as to enhance the freedom of the lone pair of the ring oxygen; the latter can then contribute more easily to



TABLE IVc  
SELECTED POSITIVE-ION FAB-MS DATA (%I) OF SOME DISACCHARIDES<sup>a</sup>

<i>m/z</i>	Ion	Sucrose [gly]	Turanose [gly]
127	(B)	20.7	26.6
145	(B)	29.8	37.6
149	X	19.8	24.2
151	Y	16.6	19.1
163	(B) Z	100.0	100.0
180	(A)	1.6	1.4
208	(C)	0.6	0.8
209	(D)	13.9	17.6
255	[163 + gly] <sup>+</sup>	19.5	9.6
273	[180 + gly + H] <sup>+</sup>	13.0	2.3
307	[M + H - 2H <sub>2</sub> O] <sup>+</sup>	2.5	2.6
325	[M + H - H <sub>2</sub> O] <sup>+</sup>	16.0	37.3
343	[M + H] <sup>+</sup>	25.3	2.3
361	[M + H <sub>2</sub> O + H] <sup>+</sup>	3.5	—
417	[M + gly + H - H <sub>2</sub> O] <sup>+</sup>	0.9	14.1
435	[M + gly + H] <sup>+</sup>	16.4	18.4
505	[M + 163] <sup>+</sup>	2.7	—
527	[M + 2gly + H] <sup>+</sup>	2.5	3.2
597	[M + 163 + gly] <sup>+</sup>	0.6	—
619	[M + 3gly + H] <sup>+</sup>	1.0	1.1
685	[2M + H] <sup>+</sup>	3.5	—

<sup>a</sup> See footnote at bottom of Table IVd.

the formation of the fragment ion at *m/z* 163. The increased intensity of the [163 + gly]<sup>+</sup> adduct ion at *m/z* 255 also supports this statement.

To further substantiate the importance of the nature of the matrix used, spectra of selected disaccharides were also recorded in other matrices [polyethylene glycol 200 (PEG-200) (84OMS101), diethanolamine (DEA) (82OMS386), and thioglycerol (TGLY)], in both positive and negative ions mode. The results were conclusive: *no stereochemical dependence could be seen* (83BMS50; 84MI2; 86MI2; 86MI3) with a solvent such as PEG-200 that can bind randomly to any part of the disaccharide, thus losing all the stereospecificity required to exhibit valuable differences in the fragmentation patterns of the oligosaccharides under study. A paper by Rose *et al.* suggested some stereochemical dependence of the adducts obtained when reacting stereo-isomeric monosaccharides with boric acid (83BMS512). This was, to our knowledge, the very first report indicating some stereochemical effects in FAB-MS of saccharides, although they report data for only four pentoses in their cautious claim.

As a last evidence of the stereochemical effect in FAB-MS of disaccharides, attention is drawn to the spectra recorded on a glycerol support, in presence or

TABLE IVd  
SELECTED POSITIVE-ION FAB-MS DATA (%I) OF SOME DISACCHARIDES<sup>a</sup>

<i>m/z</i>	Trehalose	Maltose		Cellobiose		Gentiobiose	
	[gly/H <sub>2</sub> O]	[gly]	[gly/H <sub>2</sub> O]	[gly]	[gly/H <sub>2</sub> O]	[gly]	[gly/H <sub>2</sub> O]
123	13.5	26.9	31.7	59.1	67.1	8.9	9.9
127	33.4	38.0	45.6	9.6	18.3	34.4	41.1
145	75.5	73.0	84.2	16.4	37.9	81.5	90.4
149 X	31.3	53.1	43.9	56.5	77.6	28.4	25.9
151 Y	27.5	42.3	38.0	50.9	69.0	24.8	24.4
153	13.2	22.6	27.5	55.9	62.4	7.3	8.5
163 Z	100.0	100.0	100.0	17.3	51.0	96.3	100.0
167	15.1	27.6	29.4	57.1	58.2	9.5	11.7
180	2.5	—	2.4	—	3.1	1.9	—
183	—	37.6	44.1	100.0	100.0	12.3	13.1
208	0.9	2.4	1.9	2.1	3.3	—	1.4
209	18.8	35.2	21.3	26.9	44.9	21.7	17.9
215	6.8	16.9	17.2	50.0	56.9	5.6	4.4
255	47.1	52.8	41.6	10.8	18.5	33.6	27.8
275	4.3	11.3	10.1	37.8	37.8	3.4	2.8
325	77.1	97.6	85.2	8.5	47.9	100.0	82.1
343	15.7	15.0	11.0	4.1	19.3	53.2	33.3
417	1.4	8.0	5.4	—	2.5	3.1	1.4
435	41.0	61.7	34.7	5.0	31.2	22.0	11.9
505	4.4	2.8	1.6	—	—	3.1	1.8
527	3.7	8.6	4.5	—	6.3	3.7	1.1
685	13.0	19.0	12.7	—	3.6	14.7	6.9

<sup>a</sup> —, Not detected; spectra are corrected for matrix background; [gly] indicates spectra recorded in glycerol; [gly/H<sub>2</sub>O] indicates spectra recorded in a glycerol/water mixture; A, B, C, and D refer to the general mechanisms (Fig. 9); X, Y, and Z refer to structures presented at bottom of Table II.

not, of water. The reasoning here lies on yet another analogy to the solution chemistry of disaccharides: if the production of fragment ions of pattern B occurs via the hydrolysis-like mechanism B depicted in Fig. 9, then the addition of water to the glycerol should affect considerably the overall fragmentation of the disaccharides. This was found to be the case (Table IV) (87UP1; 87UP2), as the water molecules compete directly with both (1) the glycerol for the protonation of the disaccharides, and (2) the intramolecular hydrogen-bond formation (Fig. 11); this yielded spectra in which mechanism B was enhanced for  $\beta$  anomers and reduced for  $\alpha$  anomers (this is representative of a more random conformation in the environment of the glycosidic bond).

Fragment ions arising from the other pathways varied similarly and the adduct ions containing glycerol were greatly reduced supporting the concept of a greater affinity for water (greater ease of binding to water) than for the

glycerol support. Thus it appears that glycerol binds itself to the disaccharide and induces a fragmentation pathway that, in turn, is stereochemically dependent since the binding sites of glycerol are of prime importance in the route the fragmentation will take. Binding of the matrix to the molecule under study is primordial to the detection (85MI2) of the molecular ion [and not dissolution as suggested in earlier work (76MI9; 81BJ401; 81MI9)] and the strength of that binding is governing, to a large extent, the degree of fragmentation (thus of structural information that can be obtained from the spectra). For example, in a survey of a series of corticosteroids, we have shown (85MI2) that glycerol was often unable to bind to the free hydroxyl groups of the steroids mainly because of steric hindrance. Thioglycerol, however, offers larger orbitals ( $3p$  versus  $2p$ ) that can reach much easier into volume of the steroid thus allowing to easily detect the molecular ion where glycerol failed. The "bond" so produced, however, is consequently weaker (greater intermolecular distance), and the spectra in thioglycerol showed much less overall fragmentation than their glycerol counterpart (85MI2). The protonated species-support matrix adduct ions are usually not present in the thioglycerol-based spectra but are quite numerous in other strongly binding solvents such as glycerol and diethanolamine, thus further supporting the above claim.

Figure 12 shows how glycerol can bind to a  $(1 \rightarrow 4)\text{-}\beta$ -linked disaccharide via the ring oxygen ( $\text{O}-5'$ ), thus preventing the involvement of mechanism B; it also depicts the impossibility for glycerol to bind to the  $\alpha$  counterpart. These statements would also hold true for any values of  $\phi$  and  $\psi$  (see Fig. 11) should there be several rotamers present, contrary to the enunciation of conformational principles made earlier, thus further reinforcing the theoretical

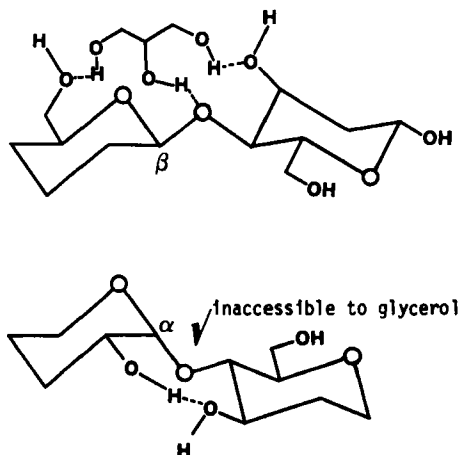


FIG. 12. Probable binding sites between glycerol and a  $(1-4)$  disaccharide.

fundamentals introduced here. Although precedents are still few, mainly due to the novelty of the technique, one report appeared suggesting a similar "charge-transfer complexation" as the ionization mechanism in FAB (83AC2195). More data are becoming available every day on the technique itself (83JCS(F1)1249), its optimization (82AC2362), and the development of new sources (83BMS94) for better reproducibility of relative abundances of ion currents in FAB (82BMS557; 83BMS489) so as to ascertain the value of these data. More specifically, data on saccharides by FAB (82JCS(F1)1291; 82OMS29; 83OMS173; 83TL2263) compare very advantageously to those obtained via other recent mass spectral techniques (80AMS1012; 82OMS346; 83OMS220; 84AC14) in all respects, be it reproducibility, structural information, molecular ion detection, cleanliness of the spectra, etc.

The negative-ion FAB spectra of these disaccharides in glycerol also show significant differences between a given pair of anomers (e.g., cellobiose versus maltose) (87UP1) and further work in that direction is in progress in our own laboratories.

## F. DISACCHARIDE GLYCOSIDES AND DERIVATIVES

This subgroup can be seen as a test for the rules just established and a means to help in assigning a priority to each one of the four factors that were just shown to govern the general appearance of a FAB spectrum. Table V presents the data obtained for  $\beta$ -phenyl lactoside (positive ion recorded in a glycerol support to which water was added). The data might appear contradictory at first sight, because of a strong ion at  $m/z$  163 normally not seen in  $\beta$ -linked disaccharides. The addition of water is responsible, in part, for this behavior. The main factor at play here, however, is the nature of the aglycone. In fact these data compare well with the previously discussed ones involving monosaccharide glycosides (Section IV,D). This actually confirms how drastically the nature of the aglycone may influence the actual spectrum.

Table VI presents the positive-ion FAB data for three peracetylated disaccharides. These compounds constitute a series of disaccharides bearing a number of identical noncarbohydrate aglycones. The first point of interest is that these substances do not offer readily any site for binding to glycerol. This is clearly demonstrated by the absence of a significant pseudomolecular ion  $[M + H]^+$  at  $m/z$  679. Following the same principle, there is almost no fragmentation observed, suggesting that the glycerol-molecular substrate adduct is very weak if any. Accordingly, there are no glycerol-protonated molecular species adducts present. It was necessary to add some trace of yet another better binding solvent (water and thioglycerol) (84TH2) in order to record good spectra of cellobiose acetate and maltose acetate. Actually, the

TABLE V  
SELECTED POSITIVE-ION FAB-MS DATA (%I) FOR  
 $\beta$ -PHENYL LACTOSIDE<sup>a</sup>

$m/z$	Ion <sup>b</sup>	[gly/H <sub>2</sub> O]
123		14.8
127	(B)	17.3
145	(B)	43.8
149	X	56.8
151	Y	59.9
163	(B) Z	100.0
183	?	23.5
209	[D from 343]	40.7
215	[123 + gly] <sup>+</sup>	14.8
241	[149 + gly] <sup>+</sup>	22.2
243	[151 + gly] <sup>+</sup>	21.6
301	[209 + gly] <sup>+</sup>	7.4
307	[M + H - C <sub>6</sub> H <sub>5</sub> OH - H <sub>2</sub> O] <sup>+</sup>	4.9
325	[M + H - C <sub>6</sub> H <sub>5</sub> OH] <sup>+</sup> [B]	51.9
419	[M + H] <sup>+</sup>	46.9
511	[M + gly + H] <sup>+</sup>	14.8
603	[M + 2 gly + H] <sup>+</sup>	3.1

<sup>a</sup> Spectrum corrected for matrix background. This spectrum was recorded in a glycerol/water mixture.

<sup>b</sup> A, B, C, and D refer to the general mechanisms (Fig. 9); X, Y, and Z refer to structures presented at bottom of Table II.

only important fragment ions for these two samples occur at  $m/z$  331 (via mechanism B, Fig. 9) and at  $m/z$  169 and 109, occurring via an as yet undefined mechanism. Sucrose acetate was recorded in glycerol and a trace of ethyl acetate and in contrast exhibits a much larger fragment ion at  $m/z$  331 than at  $m/z$  169 and 109. This is easily accounted for in view of the fact that sucrose offers two ways to undergo mechanism B (Fig. 9), i.e., via O-5', the ring oxygen of the glycosyl moiety, or via O-5, the ring oxygen of the fructofuranoside moiety.

Care must be exercised not to assign  $m/z$  109 as the daughter ion of  $m/z$  169 through the obvious loss of acetic acid. In fact, a quick survey of all the possible combinations for the elemental compositions corresponding to a nominal mass of 109 and obeying the " $2n + 2$ " rules for the hydrogen-to-carbon ratio yields CHO<sub>6</sub>, C<sub>2</sub>H<sub>5</sub>O<sub>5</sub>, C<sub>5</sub>H<sub>3</sub>O<sub>3</sub>, C<sub>6</sub>H<sub>5</sub>O<sub>2</sub>, and C<sub>7</sub>H<sub>9</sub>O. None of these compositions is reasonable. Even if one was to assume that  $m/z$  109 actually comes from a doubly charged ion of 218 daltons, it would still not be possible to construct an ion according to standard rules. The fact that these ions arise in glycerol that was spiked with three other, different, solvents seems

TABLE VI  
SELECTED POSITIVE-ION FAB-MS DATA (%I) OF SOME DISACCHARIDE DERIVATIVES<sup>a</sup>

<i>m/z</i>	Ion <sup>b</sup>	Maltose acetate [gly/thiogly] <sup>c</sup>	Cellobiose acetate [gly/H <sub>2</sub> O] <sup>d</sup>	Sucrose acetate [gly/EtOAc] <sup>b</sup>
109	[C <sub>2</sub> O <sub>5</sub> H <sub>5</sub> ] <sup>+</sup>	90.2	85.9	52.6
127	[169 - CH <sub>2</sub> =C=O] <sup>+</sup>	44.6	49.8	21.8
169		100.0	100.0	66.6
271	(B)	4.1	7.7	3.4
317	[377 - CH <sub>3</sub> COOH] <sup>+</sup>	1.4	3.4	2.4
331	(B)	35.0	32.0	100.0
348	(A)	—	0.8	—
376	(C)	—	—	—
377	(D)	—	1.0	—
517	[577 - CH <sub>3</sub> COOH] <sup>+</sup>	1.1	0.7	—
559	[M + H - 2(CH <sub>3</sub> COOH)] <sup>+</sup>	4.5	0.7	—
577	[619 - CH <sub>2</sub> =C=O] <sup>+</sup>	8.7	2.2	—
619	[M + H - CH <sub>3</sub> COOH] <sup>+</sup>	19.3	3.5	—
679	[M + H] <sup>+</sup>	—	—	2.2

<sup>a</sup> Spectrum corrected for matrix background.

<sup>b</sup> A, B, C, and D refer to the general mechanisms (Fig. 9).

<sup>c</sup> [gly/thiogly] indicates spectrum recorded in a glycerol/thioglycerol mixture.

<sup>d</sup> [gly/H<sub>2</sub>O] indicates spectrum recorded in a glycerol/water mixture.

<sup>e</sup> [gly/EtOAc] indicates spectrum recorded in a glycerol/ethyl acetate mixture.

to preclude the fact that these ions would be solvent-related, although no definitive claim can be made to that effect. At best, it can only be concluded that the behavior of these disaccharide derivatives supports the claim made above for the need that binding be established in order to obtain a good spectrum and that the strength of that association will affect drastically the amount of structural information contained in the spectra (i.e., the degree of fragmentation).

## G. HIGHER OLIGOSACCHARIDES

For higher oligosaccharides the situation in terms of conformational principles is much more complex than for disaccharides (Section IV,E). In fact, even though the majority (more than 90–95%) of linkage conformations for disaccharides are shown by the conformational energy maps to be forbidden by steric considerations alone, the remaining conformational space allows significant freedom of oscillation about the bonds to the glycosidic oxygen. In solution the molecules are not normally constrained in a unique state but

oscillate around it because of collisions and thermal energy. A carbohydrate chain typically contains a large number of such linkages, and the overall shape is the result of these independent oscillations. At any instant, such a chain would show a spectrum of linkage conformations, most of them in favorable low-energy orientations, although thermal energy would also induce a few linkages to adopt much higher energy forms and a few monomer units to adopt twist, boat, and alternative chair conformations. The greater the internal freedom at each linkage, the greater the number of conformations available to each individual segment, and the less likely it will be for the chain to adopt a unique ordered shape in which each linkage is fixed close to the minimum energy form. Chain flexibility thus provides a strong entropic drive, which generally overcomes energy considerations and induces the chain to adopt disordered or random coil states in solution (73MI5; 77MI9). This influence is known as the *conformational entropy*.

Under particular circumstances, however, favorable nonbonded energy terms (hydrogen bonding, dipolar and ionic interactions, and solvent effects) can combine to fix macromolecules in ordered shapes (73MI5; 75MI1; 77MI9). For carbohydrate chains, the interactions between individual pairs of monomers are insufficient to do this, and it occurs by synergistic action of energy terms along extended sequences of the chain, which reinforce each other to outweigh the conformational entropy. Since these interactions almost invariably occur between long, *regular* sequences, the result is a helix, because any interactions favored within a particular repeating unit will also be favored for neighboring units. Ordered structures are more favored for the solid state because cooperative interactions can then operate between chains as well as within them.

This subsection deals mainly with the effect of the nature of the aglycone, when recorded on a given support matrix. Now that a theory is emerging, it is well worthwhile to analyze a few polysaccharides (Tables VII and VIII) and some higher oligosaccharides to determine the extent to which we can relate to the theory and to size the effect of the nature of the aglycone. In order to better visualize this, the results obtained for the trisaccharides and tetrasaccharide will be discussed separately from the noncarbohydrate aglycone-containing oligosaccharides.

The data presented in tables VII and VIII agree very well with the proposed model theory derived earlier from the study of disaccharides (Section IV,E). In fact, the main fragment ions are obtained from the same type of mechanisms as those presented in Fig. 9. For trisaccharides (Table VII) two glycosidic linkages are involved and influence the spectra in their characteristic way. For example, the fragment ion at  $m/z$  325 arises from mechanism B at the glycosidic bond involving the reducing end sugar and the first nonreducing sugar, whereas fragment ion at  $m/z$  163 is the result of fragmentation B at the

TABLE VII  
SELECTED POSITIVE-ION FAB-MS DATA (%I) OF SOME TRISACCHARIDES<sup>a</sup>

<i>m/z</i>	Ion <sup>b</sup>	Raffinose pentahydrate	Melezitose	tri-GLC <sup>c</sup>
117		11.1	27.3	54.7
123		8.1	28.2	12.1
127	(B)	55.1	13.7	19.5
145	(B)	63.1	24.1	39.1
149	X	27.1	79.6	59.0
151	Y	21.1	100.0	100.0
163	(B) Z	100.0	65.4	40.6
181	[A + H] <sup>+</sup>	4.6	—	—
183		11.3	37.3	19.9
195		2.1	31.6	60.5
209	(D)	16.3	63.0	50.0
241	[149 + gly] <sup>+</sup>	7.8	36.7	23.8
243	[151 + gly] <sup>-</sup>	4.9	30.8	31.3
255	[163 + gly] <sup>+</sup>	13.9	6.4	7.0
301	[209 + gly] <sup>+</sup>	1.5	12.1	9.0
325	(B)	45.7	15.0	36.7
343	[A + H] <sup>+</sup>	32.3	1.1	6.6
435	[343 + gly] <sup>+</sup>	1.0	—	2.7
487	[M + H - H <sub>2</sub> O] <sup>+</sup>	3.7	2.7	4.3
505	[M + H] <sup>+</sup>	21.8	12.6	11.7
597	[M + gly + H] <sup>+</sup>	4.2	3.5	5.9
687	[M + 5H <sub>2</sub> O + gly + H] <sup>+</sup> (!)	4.6	—	—

<sup>a</sup> Spectra recorded in a glycerol/water mixture; corrected for matrix background; —, not detected.

<sup>b</sup> A, B, C, and D refer to the general mechanisms (Fig. 9); X, Y, and Z refer to structures presented at bottom of Table II.

<sup>c</sup> *O*-β-D-Glucopyranosyl-(1 → 3)-*O*-β-D-glucopyranosyl-(1 → 4)-D-glucopyranoside.

glycosidic bond linking the two nonreducing sugars [*m/z* 487 occurs similarly for stachyose (Table VIII)]. The differences in the intensities of *m/z* 163, for example, between the three trisaccharides can be accounted as follows.

1. *Raffinose*. *m/z* 163 can be created from the cleavage of the galactose unit, from the cleavage of the fructose unit, and the sequential cleavage of the fructose (creating *m/z* 325, and that of the glucose; since all the linkages are α, this is favored) (84TH2; 86MI2; 87UP2).

2. *Melezitose*. For melezitose, however, *m/z* 163 can arise only from the cleavage of the fructose unit (α configuration) since the galactose–glucose linkage being (1 → 3) has the property to reverse the mechanism and thus does not favor mechanism B, and that despite that it is α (see disaccharides Section IV,E and Table IV).



TABLE VIII  
SELECTED POSITIVE-ION FAB-MS DATA (%I) FOR THE  
TETRASACCHARIDES STACHYOSE<sup>a</sup>

<i>m/z</i>	Ion	[gly]	[gly]	[gly/thiogly]	[gly/NaCl]
115	[gly + Na] <sup>+</sup>	n.a.	n.a.		100.0
127	[145 - H <sub>2</sub> O] <sup>+</sup>	31.1	34.1		2.2
137	[gly - H + 2Na] <sup>+</sup>	n.a.	n.a.		99.4
145	[163 - H <sub>2</sub> O] <sup>+</sup>	45.9	46.7		10.1
149	X	93.2	79.8		2.6
151	Y	71.6	73.3		2.1
153		35.1	46.1		1.7
159		—	8.2		6.9
163	(B) Z	100.0	100.0		3.2
165		28.4	34.5		9.2
167		39.2	53.2		2.1
173	[151 - H + Na] <sup>+</sup>	n.a.	n.a.		99.9
175		n.a.	n.a.		61.6
183		50.0	84.3		2.0
185		n.a.	n.a.		24.0
209	(D)	56.8	39.3		10.5
215		28.4	43.4		11.6
241	[149 + gly] <sup>+</sup>	44.6	36.0		1.4
243	[151 + gly] <sup>+</sup>	31.1	27.0		1.4
255	[163 + gly] <sup>+</sup>	16.2	17.2		8.6
265		n.a.	n.a.		79.6
307		8.1	10.9		1.5
325	(B)	31.1	30.7		13.3
333		8.1	7.9		1.1
343	[A + H] <sup>+</sup>	9.5	10.5		2.1
435	[343 + gly] <sup>+</sup>	—	1.5	—	1.1
487	(B)	6.8	7.1	29.5	1.0
505	[A + H] <sup>+</sup>	29.7	25.5	100.0	0.6
667	[M + H] <sup>+</sup>	8.1	6.4	24.2	—
684	?	—	—	28.4	—
689	[M + Na] <sup>+</sup>	n.a.	n.a.	n.a.	5.0
759	[M + gly + H] <sup>+</sup>	—	2.6	7.8	—

<sup>a</sup> Spectra corrected for matrix background; [gly] indicates spectra recorded in glycerol; [gly/thiogly] and [gly/NaCl] indicate spectra recorded in a glycerol/thioglycerol mixture (or a glycerol/NaCl mixture); blank spaces, outside mass range; —, not detected; n.a., not applicable; A, B, C, and D refer to the general mechanisms (Fig. 9); X, Y, and Z refer to structures presented at bottom of Table II.

3. *Glucose trimer*. The glucose trimer on the other hand possesses two  $\beta$  linkages, and therefore would not be expected to exhibit mechanism B but for the fact that some water was added to the sample so as to induce mechanism B. The result agrees perfectly with the previous data as the intensity of *m/z* 163 has almost reached that of melezitose.

Fragment ion at  $m/z$  325 is similar and is allowed only for raffinose since this is the only trisaccharide in this study that meets both requirements, i.e., the proper configuration at the (glucosyl) anomeric carbon and the right stereochemistry at C-2 of the fructose unit (remote stereochemistry effect).

Furthermore, linked-scan data [ $B^2/E$  type (82SIJ169)] were obtained for daughter ion at  $m/z$  163 of raffinose and indicated that fragment ion at  $m/z$  163 arises from the spontaneous unimolecular dissociation of ions at  $m/z$  325, 289 (?), 255, and 235 in the first field free region. No collision gas was used and these data do not imply that this list of parent ions is exhaustive. On the other hand, linked-scan data [ $B/E$  type 82SIJ169)] obtained for precursor ion  $m/z$  343 for raffinose indicated that, in the first field free region, fragment ion at  $m/z$  343 further decomposes into a daughter ion at  $m/z$  325 and its oxidated form at  $m/z$  323. The linked-scan data varied with time; this is interpreted as a warning when analyzing such data and it underlines the need to watch for artefacts (77OMS735). It is also indicative of the large number of processes taking place at one time in the FAB ion source.

Stachyose was used as an example of the appearance the spectra may take according to the matrix conditions in which they were recorded. Table VIII provides some examples of the results that can be obtained. Again they support some solution chemistry concepts such as preference of cationization of the molecular species over protonation (82AC2362), easier binding to thioglycerol than to glycerol (85MI2) (larger  $[M + H]^+$ ), although much weaker (less fragmentation and no adduct ions). The spectrum recorded in glycerol only shows astonishing similarities with that of raffinose (from  $m/z$  505 downward). The same statement can be made when comparing the spectrum of raffinose and that of sucrose (Table IVc) when looking at  $m/z$  343 and lower. This is indicative of the high degree of uniformity and reproducibility obtained with these compounds, and it suggests that the cleavages are sequentially performed (cf. linked-scan data discussed above) thus leading the way to further investigations on sequencing aspects in poly- or oligosaccharides. Such attempts have been made (83BMS420; 83MI7; 83MI8; 83MI9; 83SIJ232), but none of these reports made any correspondence between the fragments produced and any stereochemical implications.

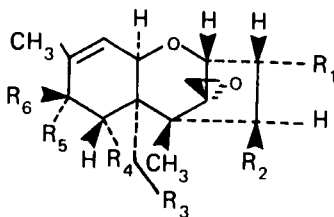
A series of higher oligosaccharides with a variety of distinct aglycones were used to investigate to which extent the fragmentation pathway taken is affected by the aglycone (84TH2). The number of aglycones, their similarities within a group, their limited variety, and the fact that it was not possible to obtain good spectra for all of them in the same solvent made it impossible to draw definite conclusions, the data being not statistically useful. However, it is possible to discern a trend; when the aglycone is a noncarbohydrate by nature, it induces a fragmentation pathway quite different that can overcome the stereochemical effects noted earlier. This appears to be true certainly for the first sugar from the aglycone, and in most cases the second one as well. After

the first two sugars, however, the effect of the nature of the aglycone seems to revert back to "normal," that is to the highly stereochemistry-dependent pattern described above. Some noteworthy examples include samples of the digoxin series which are very important in themselves and that are easily sugar sequenced (86MI2). The same holds true for some natural saponins from marine sources such as psoluthurin A and frondoside A (81TH1; 83CJC1465; 84TH1; 84TH2; 87UP3).

## V. Other Oxygen Heterocycles

Several other families of oxygen heterocycles have been studied by mass spectrometry. Unfortunately, most of the data published to date deal with the analysis of such compounds and very few reports discuss stereochemical implications (if any). Furthermore, the rather scarce data one can find on stereochemical considerations are rarely available for a series of substances forming a family as a whole. Consequently, it is difficult to draw any conclusions on these results for a given family of oxygen heterocycles. Nevertheless, some stereochemically important data can be found in several papers dealing with the mass spectra of various substances. Some of these results are summarized below along with some original data on trichothecene mycotoxins from our laboratories which are to appear shortly. Furthermore, let us refer to Mandelbaum's review (83MSR223) for pre-1980 references dealing with stereochemical effects in mass spectrometry, where several papers dealing with oxygen heterocycles are discussed in detail.

The cannabinoids have been studied in some depth (84SIJ195; 84SIJ282). The mass spectra of TMS derivatives of tetrahydrocannabinol (THC) (77MI10) and of most metabolites of the major cannabinoids give very characteristic and diagnostic ions (74HCA1626). Detailed mechanisms for their formation were elucidated using deuterium labeling (81BMS579).



**12**

The trichothecene mycotoxins, whose basic skeleton is depicted by structure **12**, have attracted considerable attention. Novel structures, including macrocycles linked through C-4 and C-15 (84ZN(C)212), have been elucidated. In our laboratories we have combined the screening abilities of FAB-MS

(85AC1470) with linked-scan techniques to demonstrate the stereochemical effects regulating the fragmentation pattern in trichothecene mycotoxins (84TH2; 87UP4). These data were correlated to those obtained by X-ray diffraction (84MI3).

The use of macrocycles such as crown ethers is also noteworthy. In most applications, use is made of those crown ethers to complex with the material under study. The so-formed aggregate is highly stereospecific (82OMS34; 82OMS651; 85CC405).

Another promising use of such oxygenated heterocycles generated *in situ* is the formation of boronate cyclic esters to establish the stereochemistry of various polyhydroxy substances. Despite some lack of success (in terms of the formation of stereochemically dependent ions) in earlier work involving FDMS (80MI7; 82T1125), Rose *et al.* obtained more success in their study of boronic acid with triols and related compounds, sugars, and nucleosides (83BMS512) where they used FAB-MS in the negative-ion mode.

One of the most complete descriptions of a stereochemical effect in mass spectrometry is the report of Tureček and Hanuš (83T1499), where they discuss at length the stereoelectronic control of the loss of a hydrogen radical from the molecular ion radical of cyclic ethers under electron-impact conditions. In that paper, results are reported on 7-oxabicyclo[4.3.0]nonanes and 2-oxabicyclo[4.4.0]decenes.

Other data on stereochemical considerations in mass spectra of oxygen heterocycles are scattered throughout the literature and often are isolated in papers dealing with other aspects of mass spectrometry so that the work is left to the reader who must scrutinize for additional information. The carbohydrates constitute really a privileged class of oxygen heterocycles. Nevertheless, a few unrelated reports are cited here for added completeness: cyclic-3',5'-phosphoranilidothioates (80OMS454), procyanidins (82SIJ110), anthranilic acids (85SIJ171), and a series of oxygen-containing aglycones (84YZ1140).

## VI. Conclusions and Future Perspectives

The amount of information available on stereochemical effects in mass spectrometry is very large. Compiling this article, however, highlighted the need for more thorough studies on given families of oxygen heterocycles. The few scattered data published to date warrant this closer examination. Carbohydrates seem to be the exception to this statement, due largely to their broad use in various applications.

Fast-atom bombardment, on the other hand, represents a totally novel and fresh approach to the concept of stereochemistry in mass spectrometry. The examples presented in this article revealed the influence of four independent

parameters that govern a FAB spectrum in terms of whether or not ions will be observed and also whether structurally useful fragment ions will be produced. With respect to carbohydrate material, these four parameters are the following.

1. *Nature of the Matrix.* It was proposed that binding of the matrix to the species under study is necessary (and not dissolution) in order to obtain a spectrum. The strength of that binding directs the degree of fragmentation that will be present in the spectrum (i.e., the amount of structural information available). The stronger the bond between the matrix and the species the more it will induce stereospecific fragmentations (85MI2).

2. *Nature of the Aglycone.* For polysaccharides, fragmentation patterns B and D (Fig. 9) are predominant (along with the protonated ionic species corresponding to mechanism A), thus supporting very strongly that, in FAB, the major ionization process is direct protonation (or cationization) and not the production of such a species via an ion radical by electron abstraction from the neutral molecular species. When the aglycone is noncarbohydrate in nature, it induces different fragmentation patterns up to at least the second sugar unit that is linked to that particular aglycone. In monosaccharide glycosides, the appearance of the spectra is almost entirely governed by the nature of the aglycone, as the aglycone represents more than one-half of the entire molecule.

3. *Configuration of the Anomeric Carbon.* The spectra are very sensitive to the configuration of the anomeric centers in the molecule. This is a truly distinctive attribute of FAB over other mass spectral techniques that should make it a powerful conformational probe if we take into account the very minute quantities required to obtain a good spectrum. This effect, however, is less important than that of the nature of the matrix. Care must be exercised therefore to choose an appropriate matrix. The sites of binding appear to be primordial, since the use of other matrices that offered limited or random binding, both in FAB and in SIMS, totally destroyed the stereochemical dependence of the spectra (82OMS386; 82TL2481; 83OMS447; 83SIJ267). Even the substitution of glycerol for PEG-200 yielded a drastic loss in stereochemical information to be derived from the spectra, and that despite the evident similarity between these matrices and a fair binding of PEG-200 to the species under study (84OMS101). The type of stereoelectronic effect regulating the fragmentation pathways taken has been suggested only once previously in the literature and it involved CI spectra of some acetate (oxygen) and was computed using MINDO/3 (82MI6).

4. *Remote Stereochemical Effect.* The stereochemistry of the various chiral centers in a given carbohydrate ring may affect the spectra. This is mainly the result of the degree of binding that can be accomplished and the number of

binding sites so offered (cf. discussion on disaccharides involving lactose and cellobiose). As such, this effect can be seen as somewhat dependent itself on the nature of the matrix. But here *nature* means the stereochemical considerations brought in by the matrix (87UP1). Although glycerol does not possess a chiral center, it offers a large number of conformers (rotamers around C—C and C—O bonds). Clearly, a more rigid matrix could not offer such a versatility in terms of binding sites to the carbohydrate structure.

Furthermore, it can be predicted that FAB will become a valuable method for the sequencing of polysaccharides. The real challenge will lie around whether or not it will be possible to correctly assign the configurations of the carbohydrate units making up the polysaccharide and the linkage points between the carbohydrate residues. In the case of oligosaccharides containing a noncarbohydrate aglycone, the task will be more difficult for the first and second carbohydrate residues directly attached to the aglycone, although there are ways of circumventing the problem (83CJC1465; 84TH1; 86MI2; 87UP3).

Questions arising from a review such as this one indicate, to some extent, the orientation of future experiments, such as the refinement of the proposed theory regarding the binding aspects of FAB so as to evaluate better matrices that will provide a good handle on the molecule of interest and will allow the analyst to literally induce fragmentation. In this laboratory it was possible to achieve this with well over 600 different substances using more than 10 different matrices. Ironically, the only compound that presented some real difficulties was a natural product (frondoside-A (84TH1; 87UP3) and the problem centered around the presence of some residual sodium salt (chloride) which was found to be responsible for the transient nature of the spectra. Future work is also necessary to show the extent to which one can use the effect of the nature of the aglycone to characterize the same (e.g., a series of steroidal glycosides, etc.). Of course, any study would be incomplete unless some definitive interpretations on the negative-ion spectra in glycerol are brought forth. The future of the technique itself seems assured.

It is impossible to conclude this discussion on FAB without mentioning the possibility of recording the spectrum of a substance directly from a thin-layer chromatography (TLC) plate (84AC109; 84UP1), as this will have direct applications (on paper chromatography) in carbohydrate analysis.

In combining this versatility in sample handling to the almost limitless number of variations possible in terms of matrices (including chiral ones, thus stressing the applications to optical stereoisomers), the organic chemist has opened the door to a totally novel and challenging area of stereochemical analysis.

It is also possible to foresee applications making use of a biological matrix to enhance, mimic, or simply monitor enzyme-like surfaces, or the like. The

advent of new solvents, especially optically active ones, is a trend likely to emerge in the very near future. In particular, the use of monoglycerol chiral esters and other biologically active materials (e.g., terpenoids) are to be expected. Similarly, the variation of the energy imparted to the fast atom beam (in FAB) is an avenue thought to be of interest to conformational studies. New techniques in sample preparation and introduction are also in the works (e.g., ultrasound) to yield more reproducible (less time-dependent) spectra. In brief, not only has mass spectrometry entered into the stereochemical studies field, it has also emerged as an innovative research tool in biological and biochemical studies, an area where it had previously been confined to the rank of an analytical method.

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